

**LONGITUDINAL STUDY OF CENTRAL MOTOR CONDUCTION
AS A PREDICTOR OF FUNCTIONAL RECOVERY
AFTER STROKE**

**A thesis for the degree of Doctor of Medicine
submitted to the University of Newcastle upon Tyne**

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by

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DEDICATION

To Janet and Alexander

ACKNOWLEDGEMENTS

This work was conducted during the tenure of the post of Research Associate in the Human Motor Research Group, Division of Clinical Neuroscience, University of Newcastle upon Tyne, during the period of October 1988 to September 1991. The study was based at the Royal Victoria Infirmary and included investigations performed at Newcastle General Hospital and Freeman Hospital all within the city of Newcastle upon Tyne.

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MEMORANDUM

In fulfilment of the requirements for the degree of Doctor of Medicine this memorandum outlines the extent to which the work contained in this dissertation is my own work.

The concept of using central motor conduction after stroke was originally set out in a grant application by my principal supervisor Professor Simon Miller but the design, organisation and administration of the study were performed by myself. I recruited all the subjects, interviewed and examined them. All the clinical assessments and neurophysiological studies were performed by myself. I was blind to the interpretation of the CT scans which was performed by Dr. Niall Cartlidge, and Dr. David Bates, both consultant neurologists and Dr. Keith Hall, consultant neuroradiologist. The data handling and statistical computing was performed by myself and a medical statistician, Mrs. Joyce French. The interpretation of the findings and the writing of subsequent scientific publications stemming from the project were in collaboration with Professor Simon Miller with contributions from the other aforementioned doctors and Mrs. Joyce French.

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ABSTRACT

Central motor conduction was assessed as a predictor of mortality and functional outcome in a longitudinal study of 118 patients with first-ever stroke. Investigations commenced 12-72 hours after stroke and were repeated up to death or 12 months. The results were compared with normal data, validated assessments of motor function, detailed neurological examinations and CT scans.

Responses were recorded in the surface electromyogram from proximal and distal muscles of both upper limbs following percutaneous electromagnetic stimulation of the motor cortex (muscles contracted) and spinal motor roots (muscles relaxed). Central Motor Conduction Time (CMCT) was estimated by subtracting the latencies of spinal root evoked responses from those of cortical evoked responses. The durations and thresholds of the responses were recorded.

Investigations 12-72 hours after stroke identified patients with 1) normal CMCT, 2) delayed CMCT, and 3) absent responses. Sequential investigations up to 12 months after stroke revealed 1) CMCT may remain unchanged, 2) delayed CMCT may become normal 3) responses may reappear with shortened duration, with delayed or normal CMCT, 4) responses were lost if the stroke extended, 5) initially high thresholds to stimulation decreased.

Absent responses 12-72 hours after stroke initially correlated with reduced power, hand dexterity and functional ability, and with large infarctions, mass effect and cortical lesions on CT scans. Normal CMCT correlated with a high probability of survival and significantly better functional recovery at 12 months. Absent responses correlated with a high probability of stroke-related death. Survivors had

poor outcome for muscle power, hand dexterity, activities of daily living, functional outcome and duration of stay in hospital.

Results from the thenar muscles alone provided accurate prognostic information. If results from all the muscles were considered and the test repeated seven days after the first assessment, the sensitivity of the test increased.

Electromagnetic stimulation is a safe prognostic investigation that is complementary to clinical examination and imaging patients with stroke.

ABBREVIATIONS AND DEFINITIONS

CMCT	Central motor conduction time
CT	Computerised tomography
EMG	Electromyogram
EMS	Electromagnetic stimulation
ES	Electrical stimulation
Kruskal-Wallis	Kruskal-Wallis one-way analysis of variance
LACS	Lacunar syndrome
MEP	Motor evoked potential
Mann-Whitney	Mann-Whitney U - Wilcoxon rank sum W test
MRI	Magnetic resonance imaging
NR	No response
NS	Not significant
PACS	Partial anterior circulation syndrome
POCS	Posterior circulation syndrome
SEP	Sensory evoked potential
SD	Standard deviation
TACS	Total anterior circulation syndrome
Wilcoxon	Wilcoxon matched pairs signed ranks test

Paretic side of body:

Side of greater motor impairment.

Non-paretic side of body:

Side contralateral to paretic side.

Damaged hemisphere:

Hemisphere contralateral to paretic side.

Undamaged hemisphere:

Hemisphere contralateral to non-paretic side.

Normal Response Group:

Group of patients who showed normal CMCT values obtained with respect to responses in thenar muscles.

Delayed Response Group:

Group of patients who showed delayed CMCT values obtained with respect to responses in thenar muscles.

No Response Group:

Group of patients with no responses in thenar muscles to maximal electromagnetic stimulation of the cortex.

Patients with responses:

Patients who have responses in the target muscles following electromagnetic stimulation of the motor cortex. (Normal and Delayed Response Groups combined).

Immediate post-stroke period:

Within 72 hours of the first symptom due to the stroke.

CONTENTS

CHAPTER 1: INTRODUCTION.

1.1 THE INDIVIDUAL AND FINANCIAL COST OF STROKE.

1.2 PREDICTORS OF OUTCOME AFTER STROKE.

1.2.1 Clinical findings of prognostic value.

1.2.2 CT scan features immediately after stroke.

1.2.3 The need for further research into methods of prognostic value.

1.3 ELECTRICAL STIMULATION OF THE BRAIN.

1.4 ELECTROMAGNETIC STIMULATION OF NEURAL TISSUES.

1.4.1 Development of electromagnetic neural stimulators.

1.4.2 Safety of electromagnetic stimulation of the brain.

The physical effects of imparting energy to the brain.

Cardiovascular considerations.

The risks of provoking epileptic seizures.

Effect upon cognitive function.

Hormonal changes.

Acoustic hazards.

1.5 THE USES OF ELECTROMAGNETIC STIMULATION OF THE BRAIN.

In neurological conditions with motor impairment.

What neural elements are excited by electromagnetic stimulation?

1.6 NEUROPHYSIOLOGICAL INVESTIGATIONS AFTER STROKE.

Electrical stimulation of the brain.

Sensory evoked potentials.

Electromagnetic stimulation of the motor cortex.

1.7 AIMS OF THE PROJECT.

CHAPTER 2: METHODS AND MATERIALS.

2.1 STRUCTURE OF THE PROJECT.

2.1.1 Normal subjects.

2.1.2 Patients.

2.1.3 Definition of stroke.

2.1.4 Inclusion criteria.

2.1.5 Clinical details recorded.

2.1.6 The timing of investigations after stroke.

2.2 RADIOLOGICAL, CLINICAL AND NEUROPHYSIOLOGICAL ASSESSMENTS OF PATIENTS WITH STROKE.

2.2.1 Initial and sequential assessments.

2.2.2 Outcome assessments at 12 months.

2.2.3 Radiological assessments.

2.2.4 Clinical assessments.

Symptoms.

The Bamford Classification of stroke.

Examination of tone and tendon reflexes.

The Motricity Index of muscle power.

The Nine Hole Peg Test of hand dexterity.

The Barthel Scale of the activities of daily living.

The Barthel scale of the activities of daily living at 12 months.

The Rankin Scale of functional outcome at 12 months after stroke.

2.2.5 Mortality after stroke.

2.2.6 Period of time to death.

2.2.7 Duration of stay in hospital after stroke.

2.2.8 Neurophysiological assessments.

Electromagnetic Stimulation of the brain.

Electromagnetic stimulation of the motor cortex.

Threshold of stimulation of the motor cortex.

Recording of the surface electromyogram.

Protocol for electromagnetic stimulation of the motor cortex.

Electromagnetic stimulation of the spinal roots.

Central Motor Conduction Time (CMCT).

Duration of the motor evoked potential.

Accuracy and objectivity of estimations of CMCT.

2.3 ASSESSMENTS OF NORMAL SUBJECTS.

2.4 PILOT CROSS-SECTIONAL STUDY.

2.5 DATA HANDLING AND STATISTICS.

Validity of measures of CMCT in predicting outcome at 12 months.

CHAPTER 3: RESULTS.

3.1 PILOT CROSS-SECTIONAL STUDY.

3.2 NORMAL SUBJECTS.

3.2.1 Handedness.

3.2.2 The Nine-hole Peg Test of dexterity in normal subjects.

3.2.3 Electromagnetic stimulation in normal subjects.

CMCT and duration of response.

Threshold to stimulation.

3.3 STROKE PATIENTS.

Timing of the first investigations after stroke.

Exclusions prior to entry to study.

Exclusions following entry to study.

Patient compliance.

Handedness and side of weakness after stroke.

3.4 NEUROPHYSIOLOGICAL RESULTS AT DAY 1 IN STROKE PATIENTS.

3.4.1 CMCT estimated from responses recorded in the paretic arm following EMS of the damaged hemisphere at Day 1.

3.4.2 CMCT and duration of the response in the non-paretic arm following EMS of the undamaged hemisphere at Day 1.

3.4.3 Threshold of responses following EMS of the damaged and non-damaged hemispheres at Day 1.

3.5 CENTRAL MOTOR CONDUCTION IN THE FIRST 12 MONTHS AFTER STROKE.

3.5.1 Changes in CMCT from responses recorded in the paretic arm during the first 12 months after stroke.

3.5.2 Evolution and severity of stroke.

3.5.3 Changes in the duration of responses recorded in the paretic arm during the first 12 months after stroke.

3.5.4 Threshold to electromagnetic stimulation of the motor cortex after stroke.

3.6 SAFETY OF ELECTROMAGNETIC STIMULATION FOLLOWING STROKE.

Symptoms following EMS of the brain.

Incidence of epileptic seizures.

3.7 RADIOLOGICAL AND CLINICAL ASSESSMENTS AFTER STROKE

3.7.1 CT scanning after stroke.

The relationship of CT scan features to central motor conduction.

3.7.2 Symptoms after stroke.

The relationship of symptoms with central motor conduction.

3.7.3 The Bamford clinical classification of stroke.

The relationship of the Bamford classification of stroke with central motor conduction.

3.7.4 Muscle tone and tendon reflexes after stroke.

Examination of muscle tone and tendon reflexes at Day 1.

Examination of muscle tone at 12 months after stroke.

The relationship of muscle tone with central motor conduction.

Examination of tendon reflexes at 12 months after stroke.

The relationship of tendon reflexes with central motor conduction.

3.7.5 The Motricity Index of muscle power after stroke.

The Motricity Index at Day 1.

The Motricity Index at 12 months after stroke.

The relationship of the Motricity Index with central motor conduction.

3.7.6 The Nine-hole Peg Test of hand dexterity after stroke.

The Nine-hole Peg Test at Day 1.

The Nine-hole Peg Test at 12 months after stroke.

The relationship of the Nine-hole Peg Test to central motor conduction.

3.7.7 The Barthel scale of the activities of daily living after stroke.

The Barthel scale at Day 7.

The Barthel scale at 12 months after stroke.

The relationship of the Barthel scale at 12 months after stroke to central motor conduction.

3.7.8 The Rankin scale of functional outcome at 12 months after stroke.

The relationship of the Rankin scale to central motor conduction.

3.7.9 Mortality after stroke.

The relationship of mortality after stroke to central motor conduction.

3.7.10 The period of time after stroke to death.

3.7.11 The duration of stay in hospital after stroke.

The relationship of duration of stay in hospital after stroke to central motor conduction.

3.8 THE INFLUENCE OF STROKE PROGRESSION ON OUTCOME AT 12 MONTHS.

3.9 THE INFLUENCE OF THE NUMBER OF MUSCLES WITH NO RESPONSES FOLLOWING CORTICAL STIMULATION ON OUTCOME AT 12 MONTHS.

3.10 THE RELATIONSHIP OF THRESHOLD TO ELECTROMAGNETIC STIMULATION ON OUTCOME AT 12 MONTHS.

3.11 REASSESSMENT OF SURVIVORS AT 18 MONTHS.

3.12 VALIDITY OF CMCT AS A PREDICTOR OF OUTCOME.

3.13 SUMMARY OF THE RESULTS RELATING TO THE PROGNOSTIC VALUE OF ASSESSING CENTRAL MOTOR CONDUCTION AFTER STROKE.

Central motor conduction.

Absent responses.

Delayed central motor conduction time.

Normal central motor conduction time.

The role of muscle contraction during the recording of responses.

Specificity and sensitivity.

CHAPTER 4: DISCUSSION.

4.1 OBSERVATIONS IN NORMAL SUBJECTS.

4.2 OBSERVATIONS IN STROKE PATIENTS.

4.2.1 Comparison to other neurophysiological studies after stroke.

4.2.2 The importance of identifying responses in the immediate post-stroke period.

4.2.3 Responses with delayed CMCT.

4.2.4 Responses obtained following stimulation of the undamaged hemisphere.

4.2.5 The significance of the present study.

4.3 THE REASONS FOR CHANGES IN CENTRAL MOTOR CONDUCTION.

4.3.1 The pathophysiology of absent responses.

4.3.2 The anatomical basis of absent responses.

4.3.3 The mechanisms underlying delayed central motor conduction.

4.3.4 Altered excitability of corticospinal neurones following stroke.

4.3.5 Why should responses reappear?

4.4 ALTERATION IN THE DURATION OF RESPONSES IN PATIENTS WHO GAIN RESPONSES.

4.5 THE RELATIONSHIP OF ABNORMALITIES IN CENTRAL MOTOR CONDUCTION AND INITIAL CLINICAL ASSESSMENTS.

4.6 THE PROGNOSTIC VALUE OF MEASURING CENTRAL MOTOR CONDUCTION AFTER STROKE.

Abnormal central motor conduction after stroke.

Normal or delayed CMCT after stroke.

4.7 CLINICAL AND IMAGING METHODS OF PREDICTING OUTCOME COMPARED TO THE MEASUREMENT OF CENTRAL MOTOR CONDUCTION.

4.8 VALIDITY OF CMCT AS A PREDICTOR OF OUTCOME.

4.9 THE USE OF THE THENAR MUSCLES FOR EVALUATION OF CORTICOSPINAL INTEGRITY.

4.10 SAFETY OF ELECTROMAGNETIC STIMULATION OF THE BRAIN AFTER STROKE.

4.11 A PRACTICAL APPROACH TO THE USE OF EMS AFTER STROKE.

4.12 CONCLUSIONS.

4.13 THE FUTURE USE OF EMS FOLLOWING STROKE.

REFERENCES.

PUBLICATIONS ARISING FROM THIS THESIS.

INTRODUCTION

1.1 THE INDIVIDUAL AND FINANCIAL COST OF STROKE

Stroke is a clinical syndrome of rapidly developing clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin (Aho et al., 1980). Stroke is the third commonest cause of death in the United Kingdom (Wolf et al., 1986) with an annual death rate of approximately 100 per 100,000 of the general population (Kurtzke, 1986) and an incidence of approximately 200 per 100,000 per year (Sandercock and Warlow, 1983). Stroke is a major cause of physical and psychological disability in the community.

In terms of the financial cost to the health service, stroke is the third commonest cause for hospital admission (Garraway, 1976) and it has been estimated to consume 6% of all hospital costs and 4.6% of all NHS costs (Carstairs, 1976). The expenditure is due to the resources needed in the initial treatment and support of patients with stroke and the long hospitalisation that follows the acute event. The costs remain high for survivors in terms of the long-term commitment during rehabilitation and continuing care in the community. Individuals with stroke therefore represent a major financial burden to the National Health Service.

The personal cost to the individual with stroke is high. A stroke may restrict the blood supply to any part of the brain and produce neurological damage resulting in loss of function and disability for the individual. A wide range of impairment follows stroke including problems with cognition, communication and

motor and sensory loss. The functional consequences are many and include restriction of activities of daily living, social functioning, loss of employment, sexual and psychological problems. The survivors of stroke have a lower quality of life and have to face numerous problems from the social and financial consequences of their disability. The disruption of normal lifestyle is not restricted to the individual patient with stroke but also affects their family, caregivers and dependents.

The physical problems that follow stroke are diverse, but the paralysis of the limbs and loss of the ability to perform skilled motor activities is perhaps the most salient feature of stroke. Impairment of motor function in the upper limb is particularly disabling in view of man's highly evolved use of the hand in the use of tools, machines, communication skills and leisure activity. Although some degree of recovery can be expected after a stroke, complete recovery is uncommon. Only 4-9% of stroke patients can be expected to regain normal sensorimotor function in an arm that was originally completely paralysed (Adams and McComb, 1953; Twitchell 1951; Moskowitz et al., 1972). Up to 30% of patients with stroke do not recover any useful function of the upper limb (Bard and Hirschberg, 1965; Newman, 1972). The residual motor impairment in the upper limb represents a major cause of disability for patients with stroke.

The costs of stroke are high both in terms of the financial cost to the community and the constraints on health care resources, and due to the suffering and reduced quality of life experienced by the individual. Scientific research, to evaluate new treatment strategies, and methods of investigation to provide more accurate assessment of prognosis, are required to improve the care of patients

with stroke. This study has assessed the prognostic value of a relatively new neurophysiological method of investigating the function of the central motor pathways. The study focused upon motor function in the upper limb and how measurements of central motor conduction immediately after stroke relate to mortality and the recovery of motor function at 12 months. The value of this test of neurophysiological function needs to be viewed in relationship to pre-existing methods of assessing mortality and motor outcome after stroke. At the onset of the study the prognostic value of electromagnetic stimulation (EMS) of the brain following acute stroke was not established.

1.2 PREDICTORS OF OUTCOME AFTER STROKE

Prognostic information following stroke is important to determine the patient's individual need for physiotherapy and rehabilitation, and to give the patient and the relatives a more accurate indication of possible recovery. Advances in neuroscience have lead to the use of pharmacological agents in the acute stroke situation, for example thrombolytic agents such streptokinase, the use of aspirin or heparin, and neuroprotective drugs such as calcium antagonists and glutamate receptor blockers. Accurate prognostic information at the earliest possible stage after stroke would provide valuable data, which could be used to identify the patients requiring acute medical therapy and who might benefit from intensive rehabilitation. The information would assist in the planning and the costing of rehabilitation services and predicting the need for continued hospitalisation and nursing care. Early and accurate prognostication is needed in

order to enhance the care and management of the individual with stroke.

Diagnosis of stroke is achieved by careful clinical examination and is assisted by computerised tomography (CT) and, where available, magnetic resonance imaging (MRI). Clinical examination assesses the neurological impairment and function of the patient. Imaging the brain provides anatomical information regarding the site of the damage and pathological information by establishing if the stroke is due to haemorrhage or infarction. However, both clinical assessment and imaging provide limited prognostic information in the immediate post-stroke period (up to 72 hours after the onset of symptoms). Certain clinical syndromes and features on CT scans are associated with an increased risk of death but neither method is highly accurate in the immediate post-stroke period to predict the prospects for recovery of motor function in the upper limb.

1.2.1 Clinical findings of prognostic value

Certain physical signs following stroke are known to correlate with increased risk of death and thus are of prognostic value. Dysconjugate eye movements (Rankin, 1957; Oxbury et al., 1975; Allen, 1984), the presence of a full hemianopia (Gray et al., 1989), reduced level of consciousness (Marquarsden, 1983), leg weakness (Chambers et al., 1987) urinary incontinence (Wade et al., 1985) and swallowing difficulty (Wade and Hower, 1987a) all correlate with mortality. Recently, Bamford et al. (1991) reported the use of a clinical classification of physical signs that correlated with mortality.

In the first 72 hours after stroke the clinical signs may be of limited value in

predicting the return of motor function in the upper limb of survivors. Clinical evaluation is unable to distinguish neurological deficit due to neuronal death leading to permanent damage and loss of function, from signs due to reversible dysfunction of neural tissue and the effects of cerebral oedema where good functional recovery may develop. A further problem with clinical assessment leading to an overestimate of impairment is that objective assessment of motor function is difficult if the subject has cognitive impairment, psychological problems or sensory deficits as a result of stroke.

In the immediate post-stroke period, assuming that no other pathology occurs, the clinical signs can be used to predict good motor recovery in a fully conscious patient with a completed stroke where there is only mild impairment of motor function (Bonita and Beaglehole, 1988), assuming no further deterioration occurs. However, the converse is not so simple. Immediately after a stroke the severity of clinical signs in the upper limb may be of value in predicting the functional outcome of survivors (Wade and Hewer, 1987b; Prescott et al., 1982). However, some patients who initially exhibit severe motor impairment may eventually achieve good motor skills, despite the early clinical picture suggesting the contrary (Wade and Hewer, 1987b; Biller et al., 1990; Prescott et al., 1982). The time elapsed before recovery begins may be more significant as a prognostic indicator than the initial severity of the motor deficit (Marquarsden, 1983). As recovery evolves during the first few weeks after stroke, the presence of severe residual motor impairment becomes more accurate in predicting the final functional outcome. The clinical prognostication becomes more reliable when based upon clinical observations performed two to three weeks after a stroke, or even later.

Clinical assessment of the severity of paralysis can be imprecise and misleading and thus the relationship of clinical signs immediately after stroke to prognosis is ambiguous (Jongbloed, 1986).

1.2.2 CT scan features immediately after stroke

Imaging techniques such as MRI and CT scanning provide valuable anatomical and pathological information in stroke. MRI is not universally available in the U.K. or as sensitive at identifying haemorrhage as CT scanning. CT scanning is very accurate for identifying intracerebral haemorrhage (Paxton and Ambrose, 1974). The possibility of identifying cerebral infarction at an early stage after stroke has greatly improved with machines of higher resolution. However, hypodensity, the hallmark of infarction may take several days before it is well-defined and in the first 72 hours after stroke less than 50% of infarcts are evident as hypodensity (Mohr, 1986). Quantitative measurement of a visible lesion is difficult due to the influence of mass effect and cerebral oedema both of which may lead to an overestimate of the dimensions of the lesion due to poor definition of its boundaries. Later, as the lesion matures fogging may lead to disappearance of the lesion or if it remains visible it may lead to an underestimate of its size (Becker et al., 1979; Scriver and Olsen, 1981). The accuracy of anatomical and pathological information from imaging is variable in the very early stages after stroke and subsequently only provides subjective prognostic information in some patients.

1.2.3 The need for further research into methods of prognostic value

In the immediate post-stroke period clinical signs and CT scans are not accurate in predicting motor outcome. Anatomical information from CT scans is complementary to the assessment of functional activity of the individual derived from history and neurological examination, however, no single group of observations taken within 72 hours of stroke is accurate enough to predict the functional recovery of the individual patient at 12 months. What is presently lacking is objective neurophysiological assessment of the function and integrity of the central motor pathways. Further research is needed to establish objective neurophysiological methods of predicting outcome. The aim would be to combine the neurophysiological data with anatomical and clinical data to provide a more reliable prediction of the prospects for recovery of individual patients.

Damage to the motor cortex and the corticospinal tracts leads to loss of function of the contralateral limbs after stroke (Bach-y-Rita, 1980). It is therefore logical to evaluate the prognostic value of any method capable of assessing the integrity and function of the central motor pathways in a patient with stroke. Such a procedure would have to be safe, non-invasive and practicable. If observations of neurophysiological function are compared to validated clinical assessments of motor function and the tests are repeated sequentially during the recovery phase it may be possible to assess the relationship of how the function of the central motor pathways relates to the recovery of motor function. If correlations were found between measures of central motor conduction immediately after stroke and risk of death and clinical measures of outcome at 12 months once recovery has

ceased, it should be possible to assess the prognostic value of a new technique.

The neurophysiological mechanisms that underlie intrinsic neurological recovery of motor function after stroke are insufficiently understood. The relationship of the integrity of the central motor pathways to recovery of motor function is not defined. A number of procedures already exist for assessing the function of the central sensorimotor pathways. Direct and percutaneous electrical stimulation of the motor cortex, somatosensory evoked potentials (SEPs) and percutaneous electromagnetic stimulation (EMS) of the central motor pathways provide direct information and their use in studies in animals and patients with cerebral ischaemia, suggest that neurophysiological function of the central motor pathways is likely to correlate with functional outcome.

1.3 ELECTRICAL STIMULATION OF THE BRAIN

Electrical stimulation (ES) of the motor cortex to activate the motor pathways has been shown to produce movements in the contralateral limbs. This method is capable of assessing the integrity of the central motor pathways and thus providing prognostic information after stroke. Unfortunately the method is painful. The earliest investigations of motor function using ES involved direct stimulation of the exposed brains of animals. Electrical stimulation of the exposed motor cortex in the dog to produce movements in the contralateral limb was first achieved by Fritsch and Hitzig in 1870. Ferrier in 1875 observed contralateral movement of muscles during ES of the exposed monkey motor cortex. The first description of electrical methods to stimulate the human brain appears to be that

of Bartholow in 1874 (See Rothwell et al., 1991) who produced movements of the contralateral muscles during faradic stimulation of the exposed parts of a human brain. The anatomical and functional importance of these observations in man were defined in the work of Penfield and Jasper (1954).

However, for ethical and safety reasons neurophysiological investigation of the corticospinal pathway in man depends on the ability to stimulate the neurones of the motor cortex through the intact skull. Gualtierotti and Paterson (1954) first reported percutaneous ES of the motor cortex in baboons and human subjects using repetitive electrical shocks. In 1980 Merton and Morton succeeded in activating muscles in the hand and upper limb by applying a single, short (50 μ s), high voltage electrical pulse to the scalp above the contralateral motor cortex. This report was followed by the use of ES over the cervical and lumbar spine by Merton et al. (1982). Despite the brief stimulus the technique remains unpleasant and painful. It is because of the discomfort produced during ES that researchers such as Barker, Jalinous and Freeston in 1985 developed electromagnetic neural stimulators using the principles of electromagnetic induction (Faraday, 1839) to excite neural tissue indirectly through the intact skull without causing pain.

1.4 ELECTROMAGNETIC STIMULATION OF NEURAL TISSUES

1.4.1 Development of electromagnetic neural stimulators

The origin of using magnetic fields to stimulate neural tissues dates back to the end of the last century. In 1896 D'Arsonval first demonstrated how a changing magnetic field could stimulate neural tissue. His observations that

phosphenes could be produced by stimulation of the retina or visual cortex were independently reported by Beer in 1902. A number of investigators were able to reproduce the phenomenon (Thompson, 1910; Dunlap, 1911; Magnusson and Stevens 1911, 1914). It was not until 1965 that Bickford and Freming demonstrated muscle contraction could be produced using magnetic fields to stimulate the sciatic nerve in the frog and rabbit. Investigations using electromagnetic induction to produce a response in superficial peripheral human nerve were performed by Irwin et al. in 1970 and in human nerve and muscle by Halgren in 1973, followed by Polsen et al. in 1982(a). It was almost a century of intermittent interest and investigation before technological advances allowed the human motor cortex to be indirectly stimulated using a time-varying magnetic field.

Painless excitation of the human motor cortex was first achieved by Barker and his colleagues using electromagnetic induction (Barker et al., 1985, 1987). A magnetic field was generated with an induction coil placed above the scalp. Following the discharge of energy from an electrical capacitor a brief pulse of current flowed through the coil. The current rose and fell rapidly in its flow through the coil resulting in a time-varying magnetic field. This action follows the principle of electromagnetic induction whereby an electric current is induced in a conductor that lies within a time-varying magnetic field. The result in the brain was a motor evoked potential (MEP) that traversed the motor pathways and was detected in muscles of the upper limb as a change in the electromyogram. The technique is painless and non-invasive. The magnetic field passes through the body structures without significant attenuation. Thus, the skull is not a barrier to EMS and it is straightforward to produce responses to cortical stimulation in both

relaxed and voluntarily contracted muscles in both the upper and lower limbs. The lack of discomfort makes cortical stimulation both practical and acceptable to all age groups. The painless and non-invasive nature of the test is tolerated remarkably well by severely ill patients such as those with acute stroke.

1.4.2 Safety of electromagnetic stimulation of the brain

Safety must be a major consideration before using a new technique in human subjects whether they are normal individuals, patients with chronic neurological disorders or acutely ill patients with evolving stroke. Prior to the commencement of our project EMS of the brain was under close scrutiny regarding its safety. No serious adverse effects had been reported and the information available suggested the technique was safe. More recent studies and extensive use of EMS in thousands of patients of all age groups with many different neurological conditions have not revealed any immediate or medium-term adverse effects. Some individual researchers have received several thousand cortical stimuli with no apparent adverse effects (Barker, 1991). The Human Motor Research group in Newcastle has now tested several hundred babies, children and adults with no adverse effects (Eyre and Miller, personal communication). EMS of the human brain does appear to be safe. However at the onset of the present study there was very little information available regarding the safety of stimulating the brain of patients with evolving cerebral damage after acute stroke. As a consequence of this we adopted a very cautious approach to its use and applied rigorous safety criteria (See: 2.1 Structure of the project - Inclusion Criteria).

The physical effects of imparting energy to the brain

The energy absorbed by the cortex of the brain during EMS is only 1/100,000 the magnitude of the inducing current (Cadwell, 1990). The strength of the magnetic field of up to 2 Tesla, although more focused and time-variable, is of similar strength to the uniform fields used in MRI. Using electroconvulsive therapy as an analogy, the stimulus used in EMS is 1000 times smaller than that used for electroconvulsive therapy and the energy is about 10^6 smaller. The total energy delivered to the brain using EMS at maximal stimulus is approximately only 0.1% of the basal metabolic rate of the brain itself (Jalinous, 1992).

If metal objects are present within the brain they will be subjected to mechanical forces due to the induced currents. The effect upon small metallic objects is minimal but large metallic objects can be moved and much depends upon the dimensions of the object and its relative conductivity particularly if it is ferromagnetic (Jalinous, 1992). The induction of an electric current in a conductive material can produce heat and care must be taken if skin electrodes lie within the path of the magnetic field. During rapid-rate EMS specially designed electrodes with gaps cut in the electrode should be used. This simple measure interrupts the induced eddy currents and reduces heating in the electrode and lessens the risk of burns to the skin (Roth et al., 1992).

The presence of cardiac pacemakers or electronic implants in the brain e.g. hearing aids, must be considered as a contraindication lest the induced currents lead to malfunction.

Cardiovascular considerations

Electromagnetic stimulation of the motor cortex is unlikely to produce cardiovascular problems. Cardiac muscle has a high threshold to stimulation and is difficult to stimulate with EMS (Geddes, 1991). This is partly due to the distance that cardiac muscle lies from the skin and due to the exponential fall in magnetic field with distance. The net result is that very powerful EMS is required to interfere with the function of cardiac muscle. Experiments with EMS in rats and an anaesthetized dog have failed to cause ventricular ectopic beats (Polson et al., 1982b; Bourland et al., 1990). Similarly no significant changes in cardiovascular function in terms of heart rate, blood pressure or focal cortical blood flow were observed following repeated EMS in cats, even under conditions of severe cerebral anoxia (Eyre et al., 1990). It is therefore highly unlikely that EMS of the brain could directly interfere with cardiac function.

The risk of provoking epileptic seizures

The risk of provoking an epileptic seizure from EMS is low. The use of EMS appears to be safe in patients with seizures despite the fact that cortical excitability is increased with generalised untreated epilepsy (Reutens and Berkovic, 1992). Kindling is the phenomenon whereby an epileptic focus is induced by a stimulus. Goddard et al. (1969) were unsuccessful at inducing kindling using ES in experimental animals at stimulus frequencies of less than 3 Hz, irrespective of the total number of stimuli given. Most electromagnetic stimulators have a

maximum discharge rate of less than 0.5 Hz, hence no danger of kindling should exist (Barker, 1991). In patients with epilepsy, although it is possible to provoke electroencephalographic evidence of seizure activity, it has been very difficult to produce a clinical seizure. Hufnagel (1990a) was only able to provoke a clinical seizure in 1/13 patients with complex partial seizures. Tassinari (1990) only provoked one clinical seizure in fifty-eight patients with epilepsy and did not record any change in seizure frequency or type of attack during a three months follow-up.

Isolated seizures occurring during EMS have been reported. A focal seizure occurred in a normal subject when using rapid-rate EMS at 10Hz at 100% of maximum output (Pascual-Leone et al., 1992a). It is widely assumed that single stimuli repeated at less than 0.5 Hz are safe but, it remains possible that rapid-rate stimuli of high intensity and frequency may produce a seizure in predisposed individuals. Hömberg and Netz (1989) reported a single seizure in a stroke patient with a massive hemispheric infarction. Following this event the authors suggested that patients with large ischaemic lesions may be more vulnerable to seizures and EMS should be avoided in patients with large areas of damage. There is also a report of a focal seizure provoked by EMS in a subject with a large hemispheric infarction who was investigated 10 months after stroke (Fauth et al., 1992).

However, in view of the number of subjects investigated using EMS and only isolated reports of seizures these were likely to have been incidental occurrences. Recent studies in stroke patients did not observe a worsening of the neurological deficit or secondary effects following stimulation of the motor cortex (Kandler, 1990; Escudero et al., 1992). Experiments in animals with ischaemia did not reveal any abnormality in cerebral blood flow or cortical activity nor any increased

risk of kindling during stimulation at the time of anoxia (Eyre et al., 1990)

(See: Discussion - 4.10 Safety of EMS of the brain after stroke).

Effect upon cognitive function

Recently, transient changes in cognitive function occurring during EMS have been reported by Levy et al. (1990). The changes were within a narrow time range and were probably due to a short-lived and focal interference of cognitive processing. Delayed execution of voluntary movement has been observed after EMS of the brain in man (Day et al., 1989; Ammon and Gandevia, 1990; Andrews et al., 1992) and delayed perception of a transient visual stimulus after stimuli were given over the occipital regions (Amassian et al., 1988). In both cases, it was likely to be due to a temporary interference of processing and planning. Psychometric testing has not shown any significant changes in relation to stimulation (Rossini et al., 1987; Bridgers and Delaney, 1989) and longer term interference of cognition has not been reported. Histopathological study of surgically removed temporal lobes from patients investigated with EMS prior to surgery did not show any lesions attributable to EMS, despite the fact that the brain had been subjected to approximately 2000 stimuli (Gates et al., 1992).

Hormonal changes

No significant changes in cortisol or prolactin were observed following excitation of the human brain using EMS (Levy et al., 1990, Thomas et al., 1991).

Acoustic hazards

Finally, a more insidious hazard from EMS was suggested by Counter et al. (1990) who found the discharge noise from the magnetic coil to be surprisingly loud. Brief clicks of up to 157dB were recorded close to the ears of rabbits. The brevity of the sound and the relatively long time constant of the human auditory perception means that damaging effects could go unnoticed. Barker et al. 1991, and Boyd et al. 1991, concluded that the magnetic nerve stimulators they examined did not produce a significant acoustic hazard in normal use. A further study by Pascual-Leone et al. (1992b) did not reveal any hearing loss in human subjects but did recommend the use of earplugs for subjects and investigators.

1.5 THE USES OF ELECTROMAGNETIC STIMULATION OF THE BRAIN

In neurological conditions with motor impairment

Electromagnetic stimulation of the human motor cortex to produce MEPs recorded from the surface EMG in skeletal muscle has developed into a widely used, non-invasive technique for evaluating descending motor pathway function in man (Rothwell et al., 1987; Rossini et al., 1987; Mills et al., 1987; Koh and Eyre, 1988; Eyre et al., 1991). Abnormalities in central motor conduction have been observed in a wide variety of disorders including patients with multiple sclerosis (Hess et al., 1986), motor neurone disease (Ingram and Swash, 1987), degenerative ataxic disorders (Claus et al., 1988), hereditary motor and sensory neuropathies (Hess et al., 1987a), Parkinson's disease (Kandler et al., 1990)

hereditary spastic paraplegia (Schady et al., 1991) and Retts disease (Eyre et al., 1990). The technique has also been used to help distinguish psychogenic paralysis from organic disease (Pillai et al., 1992).

EMS has great potential as a method for monitoring the function of the central motor pathways during surgery for scoliosis (Shields et al., 1990) and cervical spondylosis (Jaskolski et al., 1989), and to investigate the basis of mirror movements (Britton et al., 1991). EMS has been used to map the human cortex (Ueno et al., 1990) and to predict the outcome of coma (Ying et al., 1992). In addition to investigations of the central motor pathways the technique has been used to investigate patients with epilepsy (Hufnagel et al., 1990b). The technique has also been used in a wide variety of conditions affecting the peripheral nervous system.

Experience of the use of EMS in the human subject of all ages is now extensive. The safe and painless stimulation of the central motor pathways and spinal motor roots is of proven value in the investigation of many motor disorders in human subjects. The production of MEPs provides a novel solution to the problem of non-invasive and painless investigation of the function of central motor pathways. The technique allows the estimation of CMCT and the measurement of the amplitude and duration of responses and the threshold to stimulate responses. MEPs can be used to analyse the relationship of a wide range of neurological disorders to motor function in the same way in which sensory and visual evoked potentials have improved our diagnostic skills. The success of using EMS in conditions with motor impairment suggest that the technique may have an important role in the investigation of cerebrovascular disease.

What neural elements are excited by electromagnetic stimulation?

There are a number of projects that have shed light on which neural elements are stimulated and how EMS compares to ES of the brain, a technique which has now become almost obsolete in human experiments with the advent of the painless method of EMS. In studies in the monkey EMS and percutaneous ES of the scalp have been shown to evoke activity exclusively in the corticospinal pathway (Edgley et al., 1989, 1990 a and b, 1992). Rothwell et al. (1991) suggested the site of stimulation from EMS was trans-synaptic with no evidence for direct stimulation of the Betz cell. However, using recordings from the pyramidal tracts in anaesthetized monkeys Edgley et al. (1990b) have suggested that the Betz cell is directly excited by EMS at threshold. At higher intensities of stimulation, the initial segment of the corticospinal neurones are activated. Anatomical imaging performed in conjunction with EMS suggests the site of stimulation is at the junction of grey and white matter (Epstein et al., 1990). By comparison, ES may directly stimulate the pyramidal tract cells (Day et al., 1989) but this form of stimulation may deeply penetrate the brain and is capable of exciting the corticospinal pathway as distal as the medullary pyramids when suprathreshold stimulation is used (Edgley et al., 1990b). This model has been assumed to apply to human studies (Burke et al., 1990).

Electromagnetic stimulation can be used to excite the spinal motor nerves as they emerge from the vertebral column, which enables the peripheral motor conduction time to be estimated in the upper limb (Barker et al., 1986; Ugawa et al., 1989). Subtraction of the latencies from motor root responses from those

following cortical stimulation, estimates Central Motor Conduction Time (CMCT) of the fastest conducting corticospinal pathway fibres (Merton et al., 1982).

The evidence in both human and non-human primate studies support the concept that EMS excites the corticospinal pathway. The technique therefore has great potential for investigating motor changes following stroke.

1.6 NEUROPHYSIOLOGICAL INVESTIGATIONS AFTER STROKE

Electrical stimulation of the brain

A number of studies have used ES to assess the function of the motor pathways following stroke. In a study of 20 patients one to 22 months after stroke Berardelli et al. (1987) used percutaneous ES of the motor cortex and observed the absence of MEPs in 17 patients and prolongation of latency in three patients. Dominkus et al. (1990) observed similar abnormalities in 33 patients within three days of acute stroke. Fourteen patients had absent responses, 13 had delayed CMCT and six patients had normal CMCT. Two months after stroke, the initial abnormalities of central motor conduction correlated with poor recovery of motor skills. By contrast, Abruzzesse et al (1991) studied 32 patients one to 60 days after lacunar stroke. Only 1 subject had absent responses in two of the three muscles tested, 18 had delayed CMCT in one or more muscles and 14 had no change in CMCT in all three target muscles.

These studies suggest the assessment of the central motor pathways after stroke may reveal information of prognostic value. Percutaneous ES of the brain, however, is painful and therefore, there are ethical questions surrounding its use

in patients following stroke, particularly within hours of the ictus when the subject may be very ill. Alternative methods to investigate the function of the central motor pathways after stroke therefore have been explored in the present study.

Sensory evoked potentials

As an alternative to ES other investigators have used SEPs to assess damage of the sensorimotor pathways in ischaemic models and patients with stroke. SEPs in animal models of ischaemia are abolished once the cerebral blood flow falls below 12 ml/100g/minute (Branston et al., 1974). Prolongation in latency of evoked potentials (Hargadine et al., 1980; Meyer et al., 1985), was only observed in white matter damage by Lesnick et al. (1984). In adult humans with stroke, depression of SEPs was observed in 24 patients (Larson et al., 1966) and Kussofsky et al. (1982) obtained similar results in 16 patients. Unfortunately both these studies do not state clearly how long after stroke the tests were performed. Zeman and Yiannikas (1989) assessed 35 patients and demonstrated that abnormalities in SEPs correlate with functional outcome, measured by length of stay in hospital and Barthel index at the time of discharge from hospital, but they did not state exactly the interval after stroke at which the tests were performed. La Joie et al. (1982) investigated 68 patients on an average of 36 days after stroke. Absent SEPs were found to correlate with poor recovery. However, the SEP assesses the integrity of the sensory component of the sensorimotor pathways, and is not a direct test of the corticospinal pathways.

When MEPs, produced by percutaneous ES of the motor cortex were

compared to SEPs in 19 patients an average of eight days after stroke (Macdonell et al., 1989), central motor conduction was observed to be within the normal range or delayed, or no responses were obtained. MEPs were found to have slightly better predictive value for motor recovery compared to SEPs.

Electromagnetic stimulation of the motor cortex

Most studies using EMS after stroke have investigated patients in the chronic phase, weeks to months after stroke and there are only a few reports of relatively small numbers of patients tested within days of the onset of symptoms. At the time of commencing the present study there was no study of a large number of patients examined within 72 hours of the ictus. The relationship of the neurophysiological findings to initial clinical assessments and anatomical and pathological information from CT scans was unclear. No study had been performed using sequential clinical and neurophysiological assessments and documented the changes that occur in the central motor pathways and how the changes relate to probability of death and functional outcome at 12 months when further recovery is unlikely.

In a preliminary study using EMS of the brain in 10 hemiparetic patients in the non-acute period Bridgers (1990) demonstrated three groups of patients, characterised by absent responses, or responses with prolonged or normal CMCT. Similar observations were made by Berradelli et al. (1991) on 20 patients one to 54 weeks following stroke. Hömberg et al. (1991) investigated 51 patients with residual disability ranging from one to 53 months following stroke. 27% of

patients had no responses following EMS and the MEPs demonstrated a wide range of latency and amplitude. Kandler et al. (1991) made similar observations in 22 patients four days after acute stroke and suggested that the amplitudes of the MEPs may relate to outcome. Since the present project was completed, Escudero et al. (1992) have reported the findings in 62 patients with acute stroke assessed at some time within the first week after stroke. Responses were absent from the upper limb in 35% of cases. The presence or absence of MEPs correlated with muscle power and function. Finally, Chu and Wu (1992) tested 28 patients one to five days after acute stroke. Using an unusual empirical method for grouping patients with absent or delayed responses and combining the results from the upper and lower limbs, they concluded that if MEPs were present the prognosis was good and if MEPs were absent the outcome was more variable. Both these last two papers studied patients with acute stroke but failed to assess large numbers of patients in the first 72 hours following the onset of symptoms. In keeping with the others studies already cited, they failed to correlate the neurophysiological findings with functional outcome at 12 months.

The studies described so far all support the view that EMS is potentially a useful method for determining prognosis after stroke but that systematic studies of large numbers of subjects, first investigated within 72 hours following the onset of symptoms are required. To clearly evaluate the prognostic value of the technique, the initial central motor conduction findings need to be compared to mortality and a comprehensive assessment of functional outcome at 12 months whereupon functional motor recovery should be complete. How far the technique might also help to monitor the progress of motor recovery also needs to be defined.

1.7 AIMS OF THE PROJECT

No longitudinal study so far reported has reinvestigated sequentially a large number of patients with stroke at fixed time intervals and observed the changes in conduction in the central motor pathways. No definitive study has compared abnormalities in central motor conduction in the first 72 hours after the onset of symptoms of the stroke to mortality and to functional outcome at 12 months. At the time of writing this thesis, the prognostic value of using EMS in the acute stroke period to determine mortality and functional outcome at 12 months was not clearly defined. The present study was therefore undertaken in order to establish the prognostic value of EMS after stroke, with the following aims:

(1) to conduct a longitudinal study on a large number of subjects following their first stroke and to make serial observations up to 12 months, starting within 12-72 hours of the onset of symptoms of stroke and thus document the natural history of conduction in the motor pathways after stroke.

(2) to compare neurophysiological measurements of conduction in central motor pathways controlling the upper limb with validated assessments of motor function, the results of detailed neurological examinations and the anatomical and pathological findings of CT scans.

(3) to assess the neurophysiological measurements as an early predictor of mortality and functional recovery at 12 months and the duration of stay in hospital.

METHODS AND MATERIALS

2.1 STRUCTURE OF THE PROJECT

The study was designed as a prospective longitudinal project and followed patients with their first-ever stroke over a 12 month period or to death, if this occurred earlier. The choice of 12 months as the outcome was based upon the observation that motor recovery after stroke is largely completed by six months (Fugel-Meyer et al., 1975). After 12 months further major functional improvement was unlikely to occur and the impairment of motor function was expected to be permanent. Survivors of the first 60 patients were also reassessed at 18 months after stroke to ensure that no further neurophysiological or functional changes continued beyond the accepted period of motor improvement. The project was preceded by a small cross-sectional pilot study in which 18 patients with their first-ever stroke were investigated at different stages of recovery. The project was approved by the Newcastle Upon Tyne University Joint Ethics Committee.

2.1.1 Normal subjects

53 healthy subjects, 20 male and 33 female, aged 47-87 years, of a similar age to the stroke patients (See below) were studied to provide normative data. (Table 1). All the subjects gave written, informed consent. These healthy volunteers were recruited from hospital visitors. Posters were placed in prominent positions within the hospital requesting the assistance of healthy subjects for stroke research.

	NORMAL SUBJECTS	PATIENTS
Total number	53	118
Males	20 (38%)	63 (53%)
Females	33 (62%)	55 (47%)
Age range, years	47-87	40-98
Mean age, years	66.5	70.8
Mean age of males	68.1	66.7
Mean age of females	65.5	75.5

Table 1. Details of the age and sex of normal subjects and patients.

2.1.2 Patients

118 patients, 63 male and 55 female, aged 40 to 98 years with first-ever stroke were recruited over a 15 month period (Table 1). The patients were recruited from the Royal Victoria Infirmary, Newcastle General Hospital and Freeman Hospital, Newcastle upon Tyne. All consultant physicians in the three hospitals gave permission to approach the patients. The patients were admitted as acute medical emergencies. Each morning, for the duration of the recruitment period, the resident medical officer for each hospital was asked about all patients admitted with the diagnosis of acute stroke. The patients were interviewed at the first possible opportunity, preferably with their relatives present. The medical notes were reviewed for evidence of previous stroke or any contraindication to EMS of the brain (See below). The purpose of the project was explained and if the patient or their relatives gave informed consent, a detailed clinical history of their symptoms was taken. Once the details of the history were available, particularly when accompanied by the account given by a relative or witness, it became apparent that many patients had sustained previous strokes and others did not have a history compatible with stroke. These patients were not recruited.

Documentation of the details of the illness was followed by neurological examination. The examination identified further patients who had not sustained a stroke. Either no signs were present, suggesting a diagnosis of transient ischaemic attack, or signs not compatible with stroke were found. A wide spectrum of non-stroke disease was discovered including simple falls in the elderly, hypotensive episodes, brain tumours, or collapses due to cardiac events or seizure.

2.1.3 Definition of stroke

Stroke was defined by the World Health Organisation criteria as a clinical syndrome of rapidly developing clinical symptoms and/or signs of focal or global loss of cerebral function with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin (Aho et al., 1980). Infarction was not distinguished from haemorrhage using clinical criteria.

2.1.4 Inclusion criteria

Patients who had sustained a stroke were considered suitable for recruitment to the study if they met the following inclusion criteria:

- 1. The patient must be admitted as an acute medical admission, and must not have sustained the stroke whilst in hospital.**
- 2. The patient must have sustained a first-ever stroke:** The patient and his/her family were questioned, but if there was any ambiguity, the patient's general practitioner was consulted. If a history of a previous stroke or transient ischaemic attack was discovered the patient was not recruited.
- 3. The patient must not be moribund:** The fitness of the patient was based upon my own observations, or those of senior medical staff responsible for the patient.
- 4. No history, or evidence of previous central neurological disease must exist:** This was to ensure that any neurological features were a consequence of stroke, and that no "contamination" from other disorders would distort the findings of the study. The only exception was migraine, assuming that no neurological deficit had

remained following the resolution of any attack.

5. No history of epileptic seizure or febrile convulsion: Seizures may reflect underlying, but clinically, covert neurological abnormalities of the brain. Excluding these patients reduced the theoretical possibility of a seizure during EMS.

6. No serious head injury or blow to the head causing a loss of consciousness: Hidden neurological damage may exist following a significant head injury and thus produce misleading and inaccurate signs. There may also be an increased risk of epileptic seizures if brain damage was present.

7. No operations that involved either a craniotomy or access to the spinal cord: This avoided the influence of post-surgical neurological damage. Also, metallic materials may have been left in-situ and, if ferromagnetic, these would have the potential for movement and heating when subjected to the time-varying magnetic field. Anatomical damage caused by these events would be potentially dangerous.

8. No atlanto-axial joint instability, e.g. from rheumatoid arthritis of the neck: Electromagnetic stimulation to the spinal roots in the cervical spine causes sudden and involuntary muscle contraction of the neck muscles. This could be potentially harmful in the presence of atlanto-axial joint instability.

9. No cardiac pacemaker or intracranial hearing devices: Such devices might malfunction in the presence of powerful electromagnetic fields and this could present a risk to the patient.

10. No history of damage to the eyes or face from metal fragments, either from shrapnel injuries or due to occupational injuries e.g. splinters from metal work: This was to avoid any potential anatomical damage to tissues. If the metal was ferromagnetic it might be displaced by the presence of the magnetic stimulus.

11. No prostheses in the head or neck e.g. in the middle ear: To avoid malfunction of electronic or electrical devices and potential movement if ferromagnetic.

12. Written informed consent must be given by the patient or from a close relative, in whose opinion it was felt that the patient would wish to participate, if he/she were able to communicate.

13. All patients must enter the study and complete their investigations within 72 hours after the onset of symptoms.

The first neurological symptom was regarded as the onset of the stroke. Patients were only recruited if the first set of investigations could be completed within 72 hours after the onset of symptoms, designated as Day 1. This was a reasonable delay during which investigations might still yield valuable and, hopefully, evolving neurophysiological findings. It allowed for the practical aspects of transporting either the equipment to the patient or the patient to the neurophysiological laboratory.

Following the initial interview and examination, if all the criteria for recruitment were met, the practical details of the project were explained to both the patient and where possible, the spouse or a close relative. If the patient demonstrated language difficulties, or problems of comprehension, e.g. confusion, the details of the project were always discussed with the next of kin or a close relative. Written consent was taken only if the patient understood or a relative was in agreement that the patient would, in their opinion, be willing to participate. If written consent could not be obtained from the patient e.g. if the patient was unable to sign their consent form, the consent was given by proxy.

I spent a lot of time explaining the details of the project to avoid misunderstandings. It was emphasized that the investigations would be repeated over a period of 18 months and at no time would these investigations hinder any treatment received whilst in hospital, nor would the tests interfere with the patients subsequent discharge from hospital, or their future placement or management. The project involved only diagnostic methods and that no therapeutic value was to be expected. There was no evidence to indicate EMS was not a safe procedure, but it was emphasised that no guarantee could be given regarding the remote possibility of unknown side effects occurring at a later date.

2.1.5 Clinical details recorded

The medical history and clinical examination findings were documented on a precoded questionnaire to allow easy transfer of the data for computing and statistical analysis. Background information about next of kin, address, general practitioner were taken and details about the onset and symptoms of the stroke, past medical history, current medications, family history, occupational history, smoking and alcohol consumption. Handedness was assessed by asking about hand preference for activities involving a high degree of dexterity such as writing, use of tools, racket games etc. The findings of the examination of the cardiovascular system were documented along with the results of a detailed neurological examination including aspects of cognitive function such as language and visual attention, fundoscopy, visual fields, the cranial nerves, sensation, muscle tone, tendon and frontal release reflexes and plantar responses.

2.1.6 The timing of investigations after stroke

The first clinical and neurophysiological investigations were completed within 12-72 hours of the onset of symptoms (Day 1). Investigations were repeated at set time intervals after Day 1, viz. 3, 7 and 28 days, 3, 6 and 12 months (Table 2), and at 18 months for the survivors of the first 60 patients recruited. Neurological assessments preceded EMS of the brain and were blind to information from CT scans. Patients too ill to be moved were assessed at the bedside since the equipment was mobile.

TIMING OF THE INVESTIGATIONS	
Day 1	within 72 hours of onset of symptoms.
Day 3	48 hours after first test.
Day 7	seven days after first test.
Day 28	28 days after first test.
Month 3	three months after first test.
Month 6	six months after first test.
Month 12	12 months after first test.
Month 18¹	18 months after first test.

TABLE 2. Timing of the neurophysiological and clinical observations.

¹ Only the survivors from the first 60 patients recruited were investigated at 18 months.

2.2 RADIOLOGICAL, CLINICAL AND NEUROPHYSIOLOGICAL ASSESSMENTS OF PATIENTS WITH STROKE

2.2.1 Initial and sequential assessments

A wide variety of clinical and neurophysiological measures of motor function and activities dependent upon motor function were assessed at Day 1 (Table 3). The details of symptoms, a complete neurological examination and the Bamford classification of stroke were only documented at the time of recruitment. When possible all other measurements were repeated at every test session. This provided a sequential record of clinical and neurophysiological change during the first 12 months of recovery.

2.2.2 Outcome assessments at 12 months

In order to define the clinical, functional and neurophysiological status of the survivors at 12 months, a range of outcome measures were used including clinical examination of tone and reflexes, assessment of muscle power in the upper and lower limbs, hand dexterity, the activities of daily living and level of independent function (Table 4). Estimates of various measures of central motor conduction were made using EMS of the brain. The number of patients who died was recorded and defined as either dying of stroke-related causes or of non-stroke death. The period of time to death and the period a patient spent in hospital were recorded. The survivors of the first 60 patients in the study were reviewed at 18 months using the same assessments to determine if further change had occurred.

INITIAL ASSESSMENTS
<p>Symptoms.</p> <p>Neurological examination.</p> <p>Bamford clinical classification of stroke.</p> <p>Examination of muscle tone and tendon reflexes.</p> <p>Motricity Index to assess limb power.</p> <p>Nine-hole Peg Test of hand dexterity.</p> <p>Barthel scale of the activities of daily living¹.</p> <p>Estimates of central motor conduction.</p>

TABLE 3. Initial assessments at Day 1.

¹ The assessment made at Day 7 was used for comparison with central motor conduction since the Barthel Scale is not reliable until about seven days.

OUTCOME MEASURES AT 12 MONTHS
Examination of muscle tone and tendon reflexes.
Motricity Index to assess limb power.
Nine-hole Peg Test of hand dexterity.
Barthel scale of the activities of daily living.
Rankin scale to assess functional outcome.
Estimates of central motor conduction:
1. CMCT
2. duration of response
3. threshold to stimulation
Mortality.
Period of time to death.
Duration of stay in hospital.

TABLE 4. Outcome measures at 12 months.

2.2.3 Radiological assessments

Scanning was performed at Newcastle General Hospital (IGE 9800 CT scanner) and at the Royal Victoria Infirmary (Shimadzu 3000TX). An attempt was made to obtain a CT scan in every patient, but eleven patients were not scanned: three patients were too ill to travel to another hospital, four patients died prior to the scan, three could not be transported for scanning due to a national ambulance strike and a further patient left hospital and did not return for a scan.

The CT scans were reviewed by two consultant neurologists and a consultant neuroradiologist who made their observations in the absence of any clinical data and the results of neurophysiological and functional assessments. The type of stroke was defined as haemorrhage if blood was visible as an area of high attenuation. Infarction was defined as a region of low attenuation. If haemorrhagic transformation of an infarction was present, the type of stroke was regarded as an infarction. If no abnormality was seen the scan was defined as normal.

If a lesion was visible its size and volume were estimated. The largest horizontal diameter in any direction of any single scan slice was measured. An approximation of the volume of the lesion was derived from multiplying the anterior to posterior depth of the lesion by its largest horizontal diameter and multiplying by the height of the lesion. This defined a cube of tissue which was approximated to spherical volume by dividing the volume by two. The final result was the approximate spherical volume of tissue affected by the lesion, the units being mm³ (Nelson et al., 1980).

The presence of ventricular rupture or hydrocephalus was noted. Mass effect was defined as displacement of anatomical structures in any plane and included sulcal effacement. The site of the lesion was identified as cortical, subcortical or both cortical plus subcortical. Laterality of lesion was defined as left, right, midline or left plus right. The pattern of the lesion was defined as confluent or patchy. The arterial territory was defined using the scheme given by Savoiardo (1986). All the features that were assessed on the CT scans are given in Table 5.

2.2.4 Clinical assessments

Symptoms

The patient or his/her carers were asked about the following symptoms: awareness of weakness in arm, leg or face, problems of swallowing, vision, speech, alteration in sensation, loss of urinary and bowel continence, loss of consciousness and headache. The side of the body affected was noted where appropriate.

FEATURES ON CT SCANS	
Type of stroke:	Haemorrhage Infarction Normal
Size:	Horizontal diameter Volume
Ventricular rupture	
Associated hydrocephalus	
Mass effect	
Site:	Cortical Subcortical Cortical + subcortical
Laterality of lesion:	Left Right Midline Left + Right
Pattern of lesion:	Confluent Patchy
Arterial territory:	Posterior inferior cerebellar artery (PICA) Basilar artery (BA) Anterior inferior cerebellar artery (AICA) Superior cerebellar artery (SPA) Posterior cerebral artery (PCA) Anterior choroidal artery (AChA) Anterior cerebral artery (ACA) Middle cerebral artery (MCA) Perforating lenticulostriate arteries (PLA) More than one territory involved
Size of lesion:	Largest horizontal diameter Approximate spherical volume

Table 5. Features identified and recorded from CT scans.

The Bamford Classification of stroke

The neurological examination findings at Day 1 were used to assign patients into four clinically defined subgroups, using the classification of Bamford et al. (1991) (Table 6). Patients were classified using this method irrespective of the type of stroke. At the time of recruitment, the nature of the insult whether infarction or haemorrhage was not defined, and only became apparent after subsequent CT scanning. Classification could be amended at Day 3 in order to accommodate any progression of signs that might have occurred. The classification was not changed at subsequent dates nor in the light of the results of the CT scan.

Examination of tone and tendon reflexes

Tone was assessed in the arms and legs for both sides of the body. The results were described as either normal, or abnormal if the tone was increased or decreased. The tendon reflexes in the upper limbs of supinator, biceps brachii and triceps brachii and in the lower limbs at the knee and ankle were assessed and were recorded as normal, or abnormal if exaggerated or absent. Plantar responses to stimulation were recorded as normal if flexor, or abnormal if extensor.

BAMFORD CLASSIFICATION OF STROKE (Bamford et al. 1991).

Total Anterior Circulation Syndrome (TACS)

Includes all the following:

- 1) Higher cerebral dysfunction
(e.g. dysphasia, dyscalculia, visuo-spatial problems).
- 2) An homonymous visual field defect.
- 3) An ipsilateral motor and/or sensory deficit involving at least two out of three areas of the face, arm and leg.

Partial Anterior Circulation Syndrome (PACS)

- 1) Only two of the three components of the TACS syndrome.
- or 2) Higher cerebral dysfunction alone.
- or 3) A motor/sensory deficit more restricted than those classified as LACS (e.g. confined to only one limb, or to face and hand but not to the whole arm).

Posterior Circulation Syndrome (POCS)

- 1) A combination of the ipsilateral cranial nerve palsy and contralateral motor and/or sensory deficit.
- or 2) Bilateral motor and/or sensory deficit.
- or 3) Disorder of conjugate eye movement.
- or 4) Cerebellar dysfunction without ipsilateral long tract deficit.
- or 5) Isolated homonymous visual field defect.

Lacunar Syndrome (LACS)

- 1) Pure motor stroke.
- or 2) Pure sensory stroke.
- or 3) Sensori-motor stroke.
- or 4) Ataxic hemiparesis, where ipsilateral cerebellar and corticospinal tract signs are present, with or without dysarthria, in the absence of higher cerebral dysfunction, or visual field deficit.

Table 6. The Bamford clinical classification of stroke (Bamford et al. 1991).

The Motricity Index of muscle power

Muscle power was recorded with the patient either seated or lying down using the Motricity Index (Demeurisse et al., 1980). This is derived from the Medical Research Council scale of power testing and uses weighted scores to assess power for six specific movements in the upper and lower limbs - pinch grip of index finger to thumb, elbow flexion, shoulder abduction, dorsiflexion of the foot, knee extension and hip flexion (Table 7). Both sides of the body were assessed at each test session.

Two principles underlie the Motricity Index, first, the strength of any one movement about a joint is similar to the strength of all other movements about the joint, and so only the strength of one movement is assessed for each joint. Second, the proportion of total recovery is represented by each change of grade, and thereby the significance of change is given by the weighted score. The weightings represent the difficulty experienced by the patient to progress from one stage to the next with the total difficulty experienced in progressing from stage 0 to stage 5. The use of weighted scores allows the calculation of a score out of 100 to represent the power at a joint, in a limb, or in the whole side.

MOTRICITY INDEX (Demeurisse et al., 1980).
<p>Pinch grip - 2.5cm cube held between thumb and index finger.</p> <p>0= no movement.</p> <p>11= any movement of finger or thumb.</p> <p>19= grips cube, but unable to hold against gravity.</p> <p>22= cube held against gravity, but not against weak pull.</p> <p>26= grips cube against gravity, but weaker than the other side.</p> <p>33= normal pinch grip.</p>
<p>Elbow flexion: elbow flexed at 90°, forearm horizontal and upper arm vertical. Patient attempts to flex arm against resistance.</p> <p>Shoulder abduction: with the elbow fully flexed and against the chest wall the patient abducts the arm against resistance.</p> <p>Ankle dorsiflexion: patient is asked to dorsiflex the foot against resistance from a relaxed plantar flexed position.</p> <p>Knee extension: extend the knee against resistance from a flexed position of 90°.</p> <p>Hip flexion: flexion of the hip from a position of 9° flexion against resistance.</p>
<p>The assessments above are scored according to the following scale:</p> <p>0= no movement.</p> <p>9= powerful contraction in muscle, but no movement.</p> <p>14= movement, but not full range and not against gravity.</p> <p>19= full range of movement against gravity, but unable to move against minimal resistance.</p> <p>25= full range of movement against resistance, but weaker than the other side.</p> <p>33= normal power.</p>
Upper limb total = (Pinch grip) + (Elbow flexion) + (shoulder abduction) + 1
Lower limb total = (Ankle dorsiflexion) + (Knee extension) + (Hip flexion) + 1
Side total = $\frac{(\text{Upper limb total}) + (\text{Lower limb total})}{2}$

Table 7. The Motricity index of muscle power (Demeurisse et al., 1980). The scores are weighted according to the difficulty of the required movement.

The Nine Hole Peg Test of hand dexterity

This is a performance test of hand function (Sharpless, 1982). The subject was asked to place nine cylindrical pegs of wood, 9mm diameter, 32mm long, into a peg board with a 3x3 array of holes spaced 50mm apart (Fig. 1). Patients performed the test using the non-paretic hand followed by the paretic hand. The time taken to position correctly all nine pegs for each hand was recorded. A time limit of 50s was applied. Less than all nine pegs may be positioned in this time or no pegs at all. The test is expressed as the rate of positioning of pegs per second. A normal range was provided by testing the normal group of 53 healthy subjects.

The rules of the procedure were explained and the method demonstrated to the patient. A practice attempt was allowed. Only the hand under investigation must pick-up the pegs. Only one peg at a time must be manipulated and it must be fully placed into a hole. If a peg was dropped, then the patient had to restart the test from the beginning with 9 pegs.

Non-motor problems may negatively influence the test and had to be compensated, e.g. positioning the peg board to one side of the midline for better performance, if hemianopia interferes with the test. If shoulder weakness limited hand positioning, the patient was allowed to lift the paretic arm into position with the non-paretic hand, but the pegs had to be grasped using the paretic hand alone.

If a cooperative patient was unable to attempt the test with the paretic hand because of other impairments (e.g. visual or cognitive) and the patient only had a flicker of movement, or no movement at all in the pinch grip component of the Motricity Index, an arbitrary score of zero pegs per second was recorded. It would

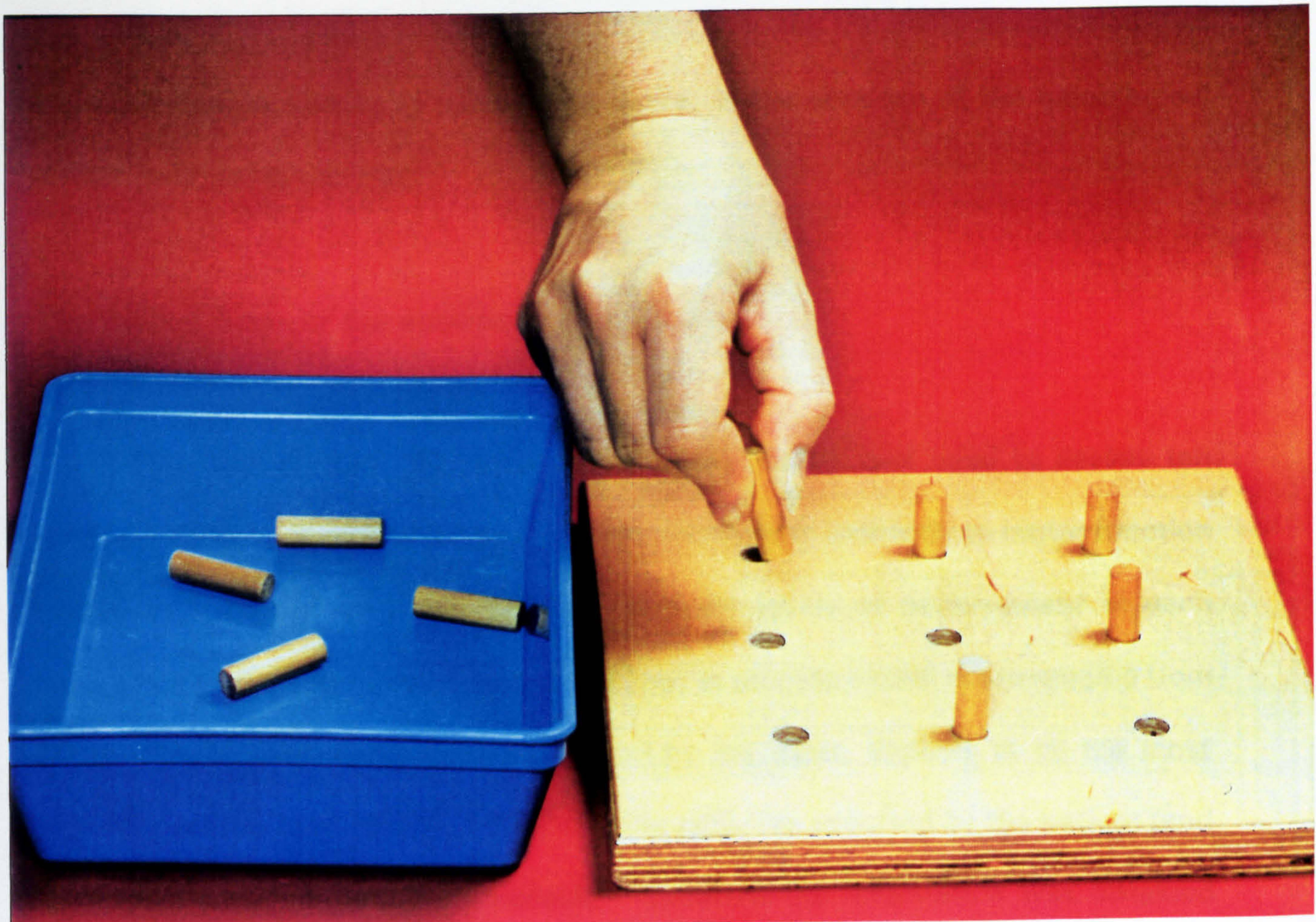


Figure 1. The Nine-hole Peg Test assesses hand dexterity. The nine wooden pegs are placed in the peg board as quickly as possible. The time taken to correctly position all nine pegs is recorded. If all the pegs are not in position within the time limit of 50 seconds the number of correctly positioned pegs is recorded. The test is expressed as the rate of peg positioning i.e. pegs/second.

seem reasonable to assume that with no useful movement in pinch grip, the hand could not be used to grasp pegs and therefore no score would be achieved. The same rule was not applied to the performance of the non-paretic hand. If movement was present, but the patient was unable to execute a skilled movement e.g. due to dyspraxia, it would not be correct to make the same assumption that the hand was incapable of achieving a score, in the absence of the neurological deficit preventing the test.

The Barthel Scale of the activities of daily living

The Barthel scale (Mahoney and Barthel, 1965) was used to assess ten different aspects of daily activity, most of which relate indirectly to motor function (Table 8). Points were awarded for different levels of achievement in each category and the scores were added together to provide a total score ranging from 0-20. The level of achievement reported by the carer, appears to be the most accurate assessment (Wade, 1985) and the activities reported by the patient tend to be less accurate and more variable. Therefore the information was obtained from the principal carer not the patient.

The activities assessed were very dependent upon motor function. This can be a weakness of the Barthel scale, but given that this study focused on motor function, the motor bias was an advantage. A disadvantage of the Barthel scale is the saturation effect of a score with a maximum of 20. The score of 20 does not equate with "normal" function and does not necessarily reflect a lack of disability, for example a problem with language secondary to a stroke can be quite

BARTHEL SCALE OF THE ACTIVITIES OF DAILY LIVING
(Mahoney and Barthel, 1965)

Bowel control	0=	incontinent
	1=	occasionally incontinent
	2=	continent
Bladder control	0=	incontinent/catheterised & unable to cope
	1=	occasionally incontinent
	2=	continent
Grooming	0=	dependent
	1=	independent for washing face; combing hair; cleaning teeth; shaving
Toilet use	0=	dependent
	1=	requires some help
	2=	independent
Feeding	0=	dependent
	1=	requires help
	2=	independent
Transfer	0=	dependent
	1=	requires major help, but can sit unaided
	2=	minor help
	3=	independent
Mobility	0=	immobile
	1=	independent with use of wheelchair
	2=	walks with the help of one person
	3=	independent (but may use stick or walking aid)
Dressing	0=	dependent
	1=	requires help with some items
	2=	fully independent
Stairs	0=	unable to climb or descend stairs
	1=	requires help on stairs
	2=	independent and able to climb or descend stairs
Bathing	0=	dependent
	1=	independent

Total = maximum of 20

Table 8. Barthel scale of the activities of daily living (Mahoney and Barthel, 1965).

disabling, but the individual can score full marks on the Barthel scale. The score must not be considered as necessarily indicative of the patient's absolute performance level - this is not possible to measure. A further potential disadvantage of the Barthel scale is the even spacing of the intervals used to measure performance. In order to lessen any adverse effects this might have on the statistical analysis of the results, non-parametric statistics have been used through the study. However, the Barthel score is a validated and useful method of assessing the activities of daily living.

At the initial interview the patient's score prior to their stroke was established. This was not necessarily the maximum of 20 points due to pre-existing problems, e.g. arthritis, or amputation of a limb. The Barthel score was assessed at every test session but the assessments at Day 1 and Day 3 have only limited value. Assessments made in the first few days are often incomplete. Patients may not have been given the opportunity to attempt some components of the scale e.g. they may have not been mobilised and therefore ability to walk and climb stairs can not be assessed, or they may have not wanted to eat, or bladder continence may be unknown. In order to allow time to assess the patient's capabilities and to provide a more accurate assessment of function, the first Barthel assessment used in any statistical comparisons was the Day 7 test. At each test session the Barthel score was expressed empirically as a score out 20.

The Barthel scale of the activities of daily living at 12 months

In addition to recording the score out of 20 at 12 months the patients were arbitrarily divided into two outcome groups - **"good"** (scores of 13 - 20) or **"poor"** (12 or less). Patients with scores of 13 or more tend to be only mildly disabled and independent of a carer for activities of daily living whereas those with scores of 12 or less tend to be dependent (Wade and Hewer, 1987b).

The Rankin Scale of functional outcome at 12 months after stroke

At 12 months functional outcome was assessed using a modified version of the Rankin scale (Rankin, 1957; Bamford et al., 1989). Six categories are recognised, ranging from 0 (no disability or symptoms and independent) to 5 (bedridden and totally dependent). Patients were assigned to different categories on the basis of their functional capacity (Table 9). Patients were also designated as **independent** (categories 0, 1 or 2), or **dependent** (categories 3, 4 or 5).

2.2.5 Mortality after stroke

If the patient died within the study, the death certificate was reviewed. Death caused by the original stroke, its extension or by further stroke was defined as stroke-related, and, unless an independent cause was identified, included death from stroke-related problems such as pneumonia, pulmonary embolus and septicaemia. Non-stroke death encompassed all other causes of death.

RANKIN SCALE (Rankin, 1957; Bamford et al., 1989).

Grade:

0 = No disability related to stroke.

1 = No significant disability.

Symptoms may be present but able to complete all usual duties.

2 = Slight disability.

Unable to complete some of previous activities, but able to look after own affairs without assistance.

3 = Moderate disability.

Requires some help, but able to walk without assistance.

4 = Moderately severe disability.

Unable to walk without assistance and unable to attend to own bodily needs without assistance.

5 = Severe disability.

Bedridden, incontinent and requiring constant nursing care and attention.

Table 9. The modified version of the Rankin scale of function
(Bamford et al., 1989).

2.2.6 Period of time to death

The number of days that a patient remained alive after stroke was recorded.

2.2.7 Duration of stay in hospital after stroke

The number of days that a patient remained in hospital or required nursing care outside of their home was recorded for survivors at 12 months. This provides a rough measure of the degree of dependence. It is clearly only a reflection of severity of stroke and is influenced by many medical, social and health care factors. It nevertheless provides information that may be useful regarding rehabilitation and medical resource management.

2.2.8 Neurophysiological assessments

Electromagnetic Stimulation of the brain

Electromagnetic stimulation was used to stimulate painlessly and safely the brain (Barker et al., 1985). A time-varying magnetic field was produced by rapidly discharging a high current through a coil held above the head of the subject with the centre of the coil placed over the vertex. The neural tissue of the brain is electroconductive and an electrical current was induced in the motor cortex. The magnetic field produced an action potential in the neural tissue and an MEP traversed the motor pathways and was recorded at the contralateral target muscle from the compound surface EMG. The patient was aware of a loud click from the

coil held above the head. This was the result of rapid expansion of the coil windings and of the gases around. The patient experienced a painless and short-lived involuntary twitch of muscles in the upper limbs.

An explanation and demonstration of the technique was given to each patient prior to the investigation and often repeated at subsequent test sessions as a reassurance that no changes had been made. Where possible a demonstration was given to the patient's relatives and to any nursing or medical staff looking after the patient. This proved to be a successful way of improving the quality of understanding regarding the technique and it minimised anxiety.

Electromagnetic Stimulation of the motor cortex

The subjects were either seated or lying half supine in bed with the particular arm being studied supported by pillows. An electromagnetic stimulator (MagStim 200, MagStim Co. Ltd.) was used to excite the motor cortex and spinal motor roots. To stimulate the motor cortex a circular coil (MagStim 9cm) was placed in the tangential plane above the vertex of the head (Fig. 2). Both sides of the coil were able to stimulate either cerebral hemisphere. The left hemisphere was stimulated with an anti-clockwise current, viewing the coil from above, and the right hemisphere by a clockwise current (Day et al., 1990). The two sides of the coil were marked so that the appropriate side was used for each hemisphere.



Figure 2. Photograph of a subject under investigation using EMS of the motor cortex.

Threshold of stimulation of the motor cortex

The output of the stimulator is graded as a percentage of maximum voltage output. The current induced in the brain is related to the power of the electrical pulse through the coil. In view of this the stimulus intensity is expressed as percentage power output of the stimulator, i.e. the square of the percentage reading of stimulus voltage displayed by the stimulator, divided by 100.

The stimulus intensity was increased gradually until the threshold level was reached, when a response in **relaxed** biceps brachii could be consistently obtained in 50% of trials. The threshold level was documented for both biceps brachii and thenar muscles, but not for triceps brachii and pectoralis major in order to reduce the total number of stimuli given to a patient. The stimulus intensity was then set at a suprathreshold level at 4% power (i.e. 20% voltage) above the threshold for biceps brachii, as far as the scale permitted. If the threshold was 100% then this was the stimulus level used. If no response was obtained, despite maximum stimulation with the target muscle relaxed, no value for the threshold to stimulation was given.

In order to document the presence of responses and to obtain appropriate values of CMCT, facilitation was provided by gentle voluntary contraction of the muscle being studied; if no voluntary contraction could be achieved, the subject contracted the homologous muscle of the opposite side (Hess et al., 1987b and c). An absent response to stimulation was documented if no response was obtained after 10 stimuli at maximum output of the stimulator and **with facilitation from muscle contraction**. Eight or more responses were recorded from stimulation

of the cortex. The **shortest latency** in any trial between cortical stimulation and the muscle response was noted, since this has been shown to provide the basis for the best estimate of central motor conduction time (Hess et al., 1987b and c). Some patients were only able to demonstrate responses by the threshold lowering effect of attempted ipsilateral or homologous contralateral muscle contraction.

Recording of the surface electromyogram

The surface electromyogram (EMG) was recorded using miniature preamplifiers with in-built electrodes applied to the skin (Johnson et al., 1977) over the following muscles bilaterally: pectoralis major (electrodes horizontally over the clavicular head); biceps brachii (electrodes in the vertical plane over the muscle belly); triceps brachii (electrodes in the vertical plane over the belly of the lateral head); thenar muscles (electrodes over the thenar eminence in the direction of the first metacarpal bone). A virtual earth electrode was applied to the forearm.

The skin was cleaned with alcohol and the area dried. The preamplifier with its two inbuilt electrodes was attached to the skin with double-sided skin-compatible adhesive tape with two holes that align with the underlying electrodes. Contact between the skin and the electrodes was made with electrode gel placed in the holes of the adhesive tape. The electrodes were placed in approximately the same position at each test session. Obviously this was not precise. Precise positioning could only have been obtained if the skin was indelibly marked to ensure the same position for the duration of the longitudinal study.

The two recording electrodes comprised silver discs of 5mm diameter set at

20mm centres. The signals were amplified and filtered with a -3dB bandpass of 10-1000Hz and recorded on magnetic tape (Racal Store 4 recorder) and also using a computer (Apricot Xi) running Signal Averager software via a type 1401 interface (Cambridge Electronic Design Ltd.). The signals from the preamplifiers were fed through an isolation circuit for safety reasons (B.S. 5247) (Fig 3). 150 milliseconds of EMG activity was recorded using the stimulus artifact as the zero point for time measurements.

Protocol for electromagnetic stimulation of the motor cortex

The clinical assessments were carried out prior to EMS. This standardised the investigations and eliminated any bias of motor function that stimulation of the motor cortex might conceivably produce. EMS was performed at every test session assuming the patient was willing, or not deemed too ill.

In stroke patients EMS of the hemisphere contralateral to the paretic side was always studied first - referred to as the damaged hemisphere. This was always followed by ipsilateral stimulation of the cervical motor roots to the same target muscles. The undamaged hemisphere was then investigated followed by stimulation of the appropriate motor roots.

The patient was repeatedly stimulated with the coil in the same position at the vertex at approximately five second intervals. Eight or more well-defined responses were recorded, unless the patient showed signs of distress, in which case, fewer stimuli were given. Such cases were rare, but if distress was encountered, e.g. if the stimulation was at maximum output, but the patient was

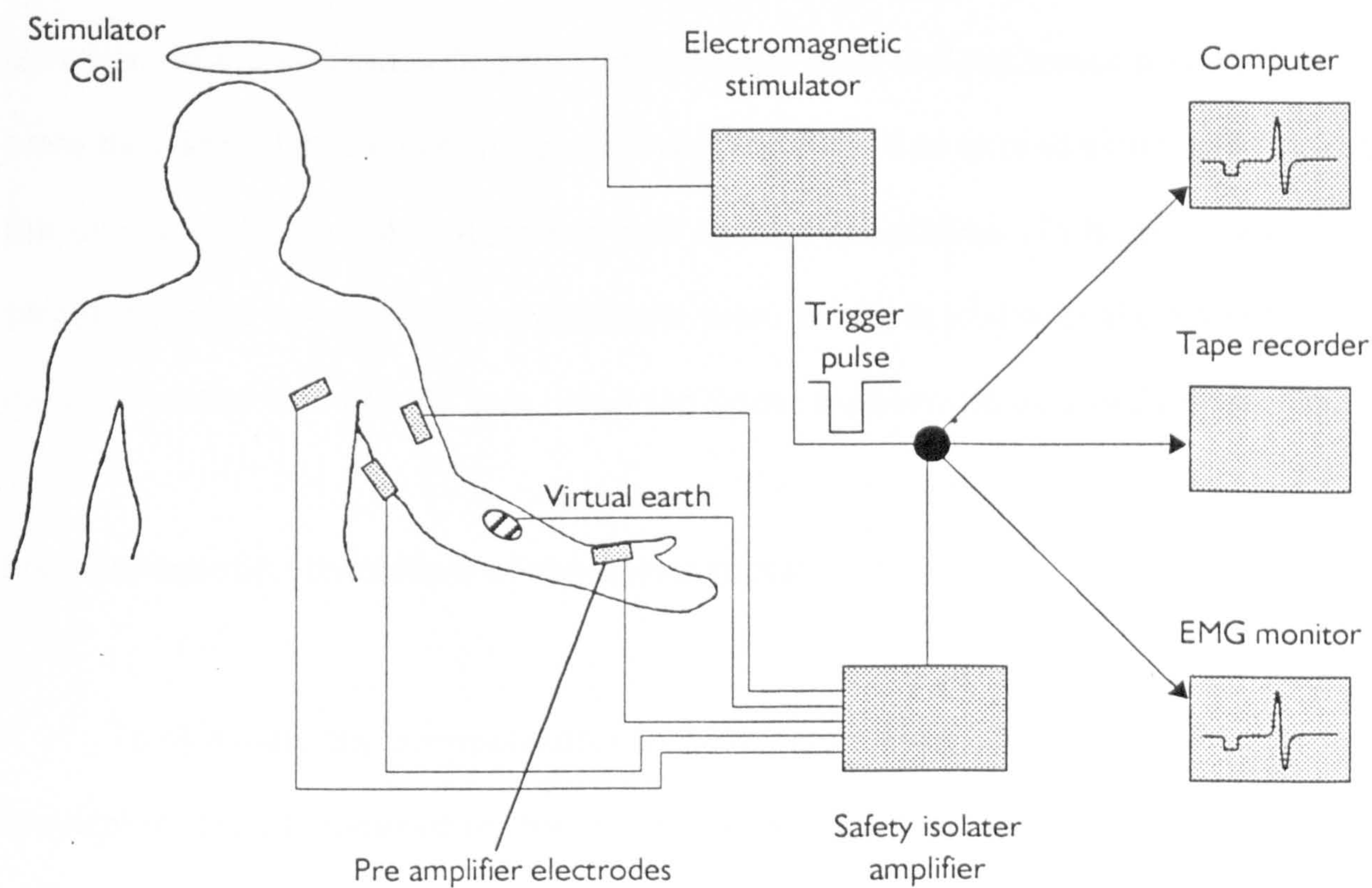


Figure 3. Diagram of the equipment used for EMS of the brain and spinal motor roots and the recording of compound EMG responses from the target muscles of the upper limb.

willing to continue, then four or more responses were recorded. If responses were absent after ten stimuli at maximum output of the stimulator and with facilitation from muscle contraction a result of "No Response" (NR) was documented. The **shortest latency** of responses following cortical stimulation was used to estimate CMCT (Hess et al., 1987c).

In order to restrict the total number of stimuli given, recordings from the thenar and biceps brachii muscles were recorded simultaneously with the muscles contracted - the biceps by attempted flexion of the elbow against resistance, whilst simultaneously contracting the thenar muscles by gripping a 3x3cm wooden cube between thumb and index finger. The triceps brachii and pectoralis major muscles were then stimulated while the patient was instructed to extend simultaneously at the elbow and internally rotate the arm against resistance. In both cases if the target muscles were paralysed attempts were made to contract the homologous muscles of the non-paretic arm using the same manoeuvre outlined above.

Electromagnetic stimulation of the spinal roots

To stimulate the cervical motor roots the stimulator coil was applied over the cervical vertebrae, centred in the coronal plane over the body of C7. Responses were recorded in the surface EMG of the target muscles. Anti-clockwise current flow was used to stimulate roots to the left arm and clockwise flow for the right arm. During stimulation of the spinal roots the target muscles were **relaxed** since muscle contraction does not affect latency when stimulating the spinal roots. The **stimulus strength was 100% power for all subjects**, irrespective of the threshold

of response. The **longest latency** was noted from eight or more responses. Four or more responses were obtained if a patient demonstrated any distress.

For stimulation of the cervical motor roots, maximum stimulation intensity at 100% irrespective of the threshold to stimulation was used for all patients and normal subjects. The decision was based upon experience gained from the pilot study described below. The use of 100% intensity provided a consistent response in the EMG. The use of supra-threshold electrical stimulation of cervical roots has been shown, however, to shorten the latency of the muscle response (Plassman and Gandevia, 1989). On the other hand supra-threshold EMS has been reported to produce responses at less variable latencies (Ugawa et al., 1989).

Since commencing the present study, further research has shown that EMS over the cervical motor roots is most consistent when applied at maximal stimulation. The best position for stimulation is to centre the coil over the midline of the cervical vertebrae. In fact, EMS appears to stimulate the motor roots more proximally than ES thus giving a more accurate estimation of CMCT (Cros et al., 1990). The method used in this project was based upon experience gained from the pilot cross-sectional study.

Central Motor Conduction Time (CMCT)

Subtraction of the **longest latency** to cervical motor root stimulation from that of the **shortest latency** to motor cortex stimulation provided an estimate of CMCT for each muscle (Hess et al., 1987c) (Fig. 4). Estimations of CMCT were made from responses from both the paretic and non-paretic limbs.

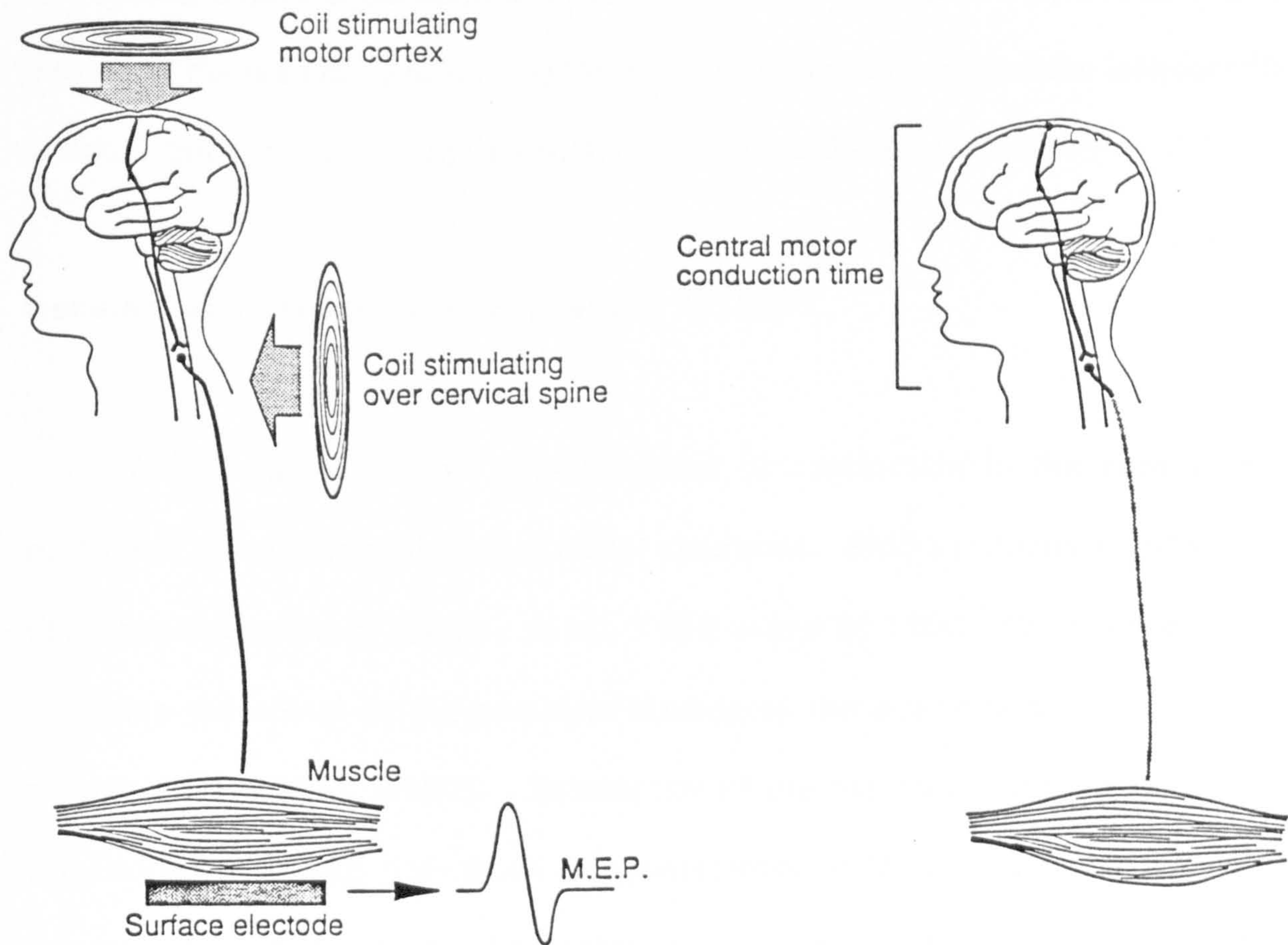


Figure 4. Diagram to demonstrate how CMCT is calculated. The longest latency of evoked potentials following stimulation of the spinal root to a particular target muscle is subtracted from the shortest latency of responses following stimulation of the cortex to the same muscle. The difference between the two responses is an estimate of CMCT.

Duration of the motor evoked potential

The durations of the responses were measured from the average of all the responses following cortical stimulation. The duration was determined visually by noting the onset of the response and where the response returned to the baseline. The measurement of duration from an average of single trials may possibly lead to a skew of the results by recording the shortest onset latency and the longest offset latency, but the inaccuracy is small in relation to the total duration.

Accuracy and objectivity of estimations of CMCT

CMCT values are an approximation of conduction in the central motor pathways synapsing with spinal motor neurones. EMS produces a volley in the corticospinal pathway (Edgley et al., 1989 a and b, 1990, 1992) which in turn activates the spinal motor neurones leading to the action potential recorded in muscle (Barker et al., 1987). Subtraction of the peripheral component from the total cortex to muscle time gives an overestimate of CMCT. EMS and ES over the cervical spine both excite the motor roots in the region of the intervertebral foramina (Mills and Murray, 1986, Schmid et al., 1990). Thus the time taken for the action potential to pass along the ventral root to its emergence from the intervertebral foramen and the corticospinal synaptic delay (approximately 1 ms) is included within the CMCT estimation (Murray, 1991). The term CMCT is therefore a useful and widely used term but it is inevitably imprecise since values of CMCT include a short peripheral component.

The onset of a response was taken as the first deflection from the baseline whether this was positive or negative. The responses were very consistent and the onset of the waveform could easily be defined and measured. All measurements of latency were analysed using a small software programme specifically written by Mr. Sean Kelly (Computing Engineer, Human Movement Research Group) for this project, which calculated the values of CMCT and duration when analysing the raw data. The longest latency following cervical motor root stimulation was subtracted from that of the shortest latency following motor cortex stimulation to provide an estimate of CMCT for each muscle.

2.3 ASSESSMENTS OF NORMAL SUBJECTS

The same contraindications for EMS for stroke patients were applied to the 53 normal subjects (Table 1). These healthy volunteers were investigated to obtain comparative data for the Nine-hole Peg Test and central motor conduction values (CMCT, duration and stimulus threshold). The nature of the investigations was explained to the subjects. All the subjects gave informed written consent. The subjects were asked about their medical history, with particular reference to cardiovascular and neurological disorders, neurological symptoms, medications, family history, smoking and drinking habits. A neurological examination was then performed. This included cognitive function; visual fields, acuity and fundoscopy; cranial nerves; peripheral sensory system; motor system; tendon reflexes, plantar response and primitive reflexes; and cerebellar function and gait. If no neurological problem was discovered, and the subjects met the same relevant safety criteria as

for the stroke patients, they were enrolled in the normal subject group.

The normal subjects performed the Nine-hole Peg Test with left hand followed by right hand. The rate for the two hands was averaged in order to eliminate the possible bias of dominance. EMS of the cortex and motor roots for both sides of the body followed, using the same methods described for stroke patients. The left hemisphere followed by the right motor roots were stimulated first, and then the right hemisphere and left motor roots. Recordings were obtained from the same four target muscles on the side of the body contralateral to the cortical stimulation using the same experimental paradigm described above. Estimates of CMCT, the duration of responses and stimulus thresholds were averaged for the homologous muscles of each side since no significant differences were identified in the responses from dominant and non-dominant hemispheres.

2.4 PILOT CROSS-SECTIONAL STUDY

Prior to the longitudinal study 18 patients with first-ever stroke, were studied cross-sectionally at different stages of recovery from 1 to 18 months after stroke using EMS of the motor cortex and spinal motor roots. These patients were selected from a study investigating risk factors leading to stroke. Their presentation and clinical features had been accurately documented by a fellow researcher, David Spriggs (Spriggs et al., 1990). All the subjects had originally presented with hemiparesis. Ten healthy normal subjects with no record of neurological disease were also investigated with EMS of the motor cortex.

2.5 DATA HANDLING AND STATISTICS

All data were tabulated on precoded forms and analysed after verification on the Northumbrian Universities Multiple Access Computer (NUMAC), using the SSPS-X statistical package. Normal ranges derived from investigations of normal subjects data are expressed as the **mean \pm 2.58 times the standard deviation** (99% confidence interval). Results from patients were considered abnormal if no recorded response was obtained despite facilitation. Values of CMCT, duration, threshold to stimulation and rate of peg positioning in the Nine-hole Peg Test were abnormal if they fell outside the 99% confidence intervals for values obtained from the normal group of subjects. **Absent responses are not regarded as a zero value.** They are not included in the calculation of any mean values (this applies to CMCT, duration and threshold). They are shown as No Responses (NR) in the figures.

All statistical comparisons used non-parametric methods. Kruskal-Wallis one-way analysis of variance was used to compare three groups of data and Mann-Whitney U test to compare two groups of data. Wilcoxon matched pairs signed rank test was used to compare paired results. Odds ratios are given as a measure of association. Where appropriate a Yates correction was used with the Chi-squared test.

Validity of measures of CMCT in predicting outcome at 12 months

The validity of CMCT in predicting outcome at 12 months has been assessed by the following statistical measures in two patient groups:

1. The No Response Group (No responses despite muscle contraction and maximal stimulator output).
2. Patients with responses (Combining the Normal Response Group and the Delayed Response Group - see Results).

Sensitivity refers to the proportion of patients with no response at Day 1 whose recovery at 12 months is graded as poor for the various outcome measures. Specificity refers to the proportion of patients with responses at normal or delayed latencies at Day 1, whose outcome at 12 months is defined as good. Positive predictive value refers to the proportion of those with no response at Day 1 whose outcome at 12 months is poor, and negative predictive value provides the proportion of those with responses at Day 1 whose outcome at 12 months is good (See Kramer, 1988).

RESULTS

3.1 PILOT CROSS-SECTIONAL STUDY

The main observations from the pilot cross-sectional study are listed below:

1. Following EMS of the cortex responses could always be obtained in relaxed muscles at thresholds below maximal stimulator output in normal subjects.
2. Cortical responses were always recordable in the non-paretic limb following stimulation of the non-damaged motor cortex in patients with stroke.
3. No ipsilateral responses could be evoked in either the normal or stroke subjects.
4. In more than half the stroke subjects responses in the paretic limb could only be obtained at maximal stimulator output (100%) facilitated by muscle contraction.
5. In three subjects no responses were obtained in the paretic upper limb despite maximal stimulation and contraction of the homologous muscles in the non-paretic upper limb.
6. It was confirmed that muscle contraction shortened the latency of the evoked response (Hess et al., 1987b).
7. Responses were always produced following stimulation of the spinal roots in both normal and stroke subjects but the stimulus strength varied greatly from as low as 16% to 100% of the power output of the stimulator. Subjects with very large neck muscles, or excessive obesity, or those with an exaggerated cervical lordosis, required maximal stimulation, presumably due to the distance from stimulator to the point of stimulation of the spinal nerve root.
8. The latency of the responses following stimulation of the spinal roots was not significantly influenced by the presence of muscle contraction.

9. The amplitude of responses were often smaller in stroke patients.
10. The amplitude of responses varied greatly within a very wide range particularly if muscle contraction was present in the limb under investigation.
11. Measurement of amplitude was very inaccurate since relaxation of muscle was particularly difficult if spasticity was present.

Following experience gained from the pilot study the following methods of investigation were chosen for the longitudinal study:

1. The threshold to stimulation would be determined in relaxed biceps brachii and thenar muscles.
2. The presence or absence of responses would be noted in relaxed muscles and in contracted muscles.
3. All recording of responses would take place during muscle contraction. The use of muscle contraction to facilitate a response ensured if a response was produced the shortest latency would be recorded.
4. Responses would be regarded as absent only if they could not be evoked after repeated attempts at maximal stimulation and with muscle contraction. This manoeuvre avoided inadvertently missing responses that were only obtained with the threshold-lowering action of muscle contraction. The use of contraction avoided problems relating to the difficulty some patients had relaxing the target muscle, particularly if spasticity was present.
5. Maximal power would be used to stimulate the spinal motor roots in order to ensure a response from all subjects.
6. Stimulation of the spinal roots did not require contraction to facilitate responses

and so responses from the motor roots would be recorded in relaxed muscles.

7. It was difficult to standardise and control the amplitude of responses. From initial trials the author concluded that measurement of amplitude was far too subjective, with too much inter- and intra-subject variation.

3.2 NORMAL SUBJECTS

3.2.1 Handedness

Handedness in the 53 healthy subjects is shown in Table 10. No correlation was found for the differences between CMCT, duration and threshold to stimulation for responses recorded from the dominant compared to non-dominant hemisphere. The constancy and reproducibility of CMCT, duration and threshold to stimulation of responses when the two hemispheres were compared meant that comparisons could be made with the results from stroke patients, irrespective of which hemisphere was affected by the stroke.

3.2.2 The Nine-hole Peg Test of dexterity in normal subjects

The peg positioning rates for left and right hands were averaged to allow comparisons with stroke patients, irrespective of the hemisphere affected by the stroke. The mean value was 0.55 pegs per second, S.D. = ± 0.07 . Any values in stroke patients that were outside the normal range were regarded as abnormal. Therefore using the results from normal subjects the normal range for the peg test rate was regarded as the mean ± 2.58 S.D i.e. the 99% confidence interval.

HANDEDNESS	NUMBER OF SUBJECTS (n = 53)	
Left	2	(4%)
Right	49	(92%)
Ambidextrous	2	(4%)

Table 10. Handedness in normal subjects.

3.2.3 Electromagnetic stimulation in normal subjects

CMCT and duration of response

Typical EMG responses to EMS of the motor cortex and the cervical motor roots are shown in Fig. 5A for normal subjects. Responses could always be obtained following EMS of the motor cortex or the spinal motor roots whether the muscles were relaxed or contracted. Responses were recorded in contracted muscles during cortical stimulation and in relaxed muscles during stimulation of the spinal roots.

The variation in latency of cortical responses to different muscles and the differences in CMCTs reflects the different intracranial distance travelled by the responses from their origins in the motor cortex to the level where the motor roots exit from the spinal cord. The results for individual muscles were very consistent. The recordings from the pectoralis major muscles demonstrated the most variation. The durations of the cortical responses are very similar for the different muscles.

The results of CMCT for all 53 normal subjects for each muscles tested are plotted against age in Fig. 6. No statistical relationship to age was found for CMCT or duration, hence all stroke patients could be compared without taking age into consideration. The mean values of CMCT and duration are given in Table 11. Therefore using the results from normal subjects the normal range for CMCT was regarded as the mean \pm 2.58 S.D i.e. the 99% confidence interval. Any values for stroke patients that lie outside the normal range were regarded as abnormal.

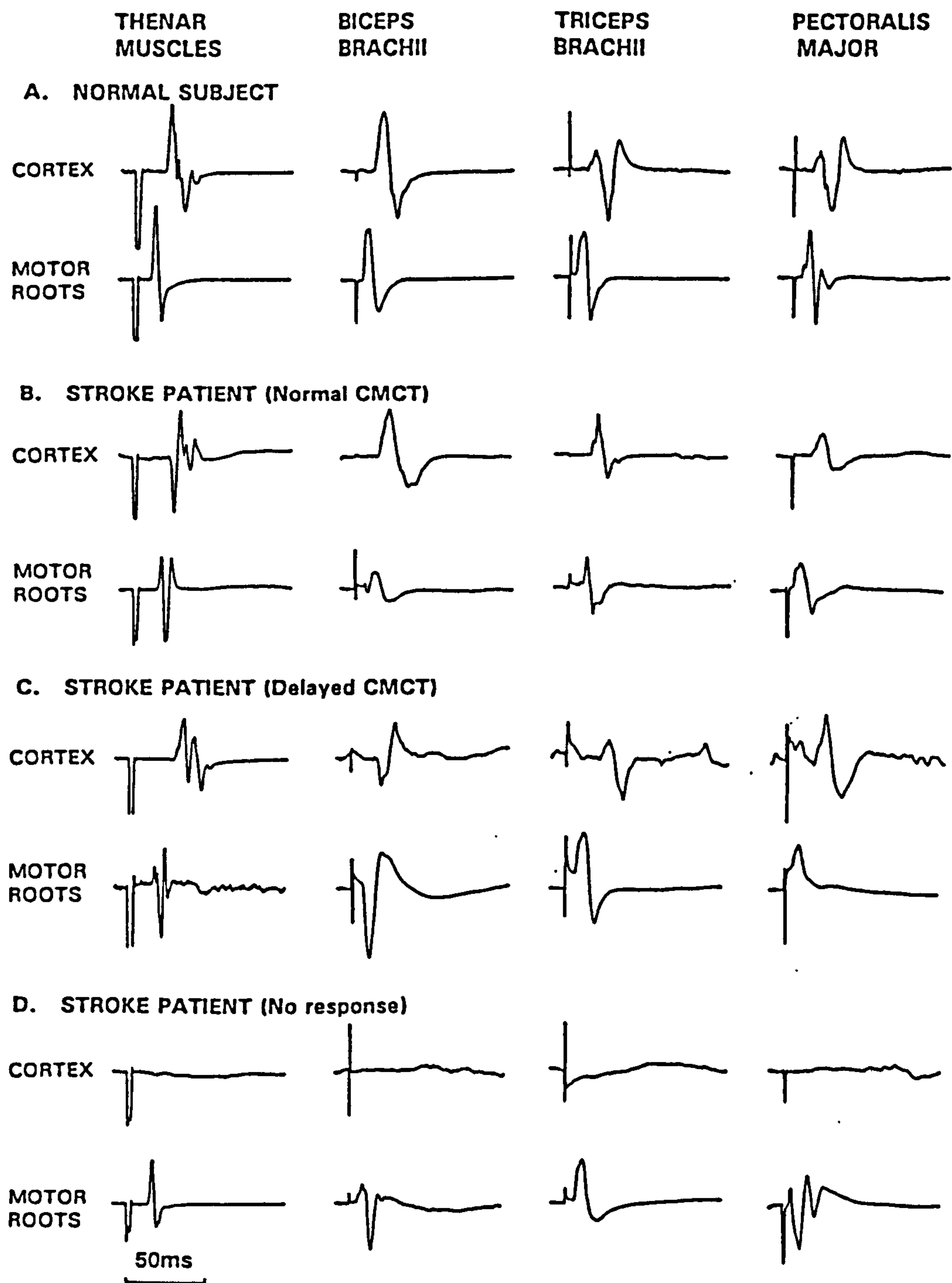


Figure 5. Responses recorded in the EMGs of different muscles following EMS of the motor cortex and spinal motor roots. The responses to cortical stimulation were recorded in the presence of muscle contraction or, if no voluntary contraction could be achieved, with voluntary contraction of the homologous contralateral muscle. The cortical stimulus intensities were set at a value of 4% power above the power at threshold for a response. Maximal stimulation was used during stimulation of the spinal roots with the target muscles relaxed.

- A** Normal subject with responses in all four target muscles with normal CMCT.
- B** Stroke patient with responses in all four target muscles with normal CMCT.
- C** Stroke patient with responses in all four target muscles with delayed CMCT.
- D** Stroke patient with no response in all muscles despite maximal EMS and muscle contraction.

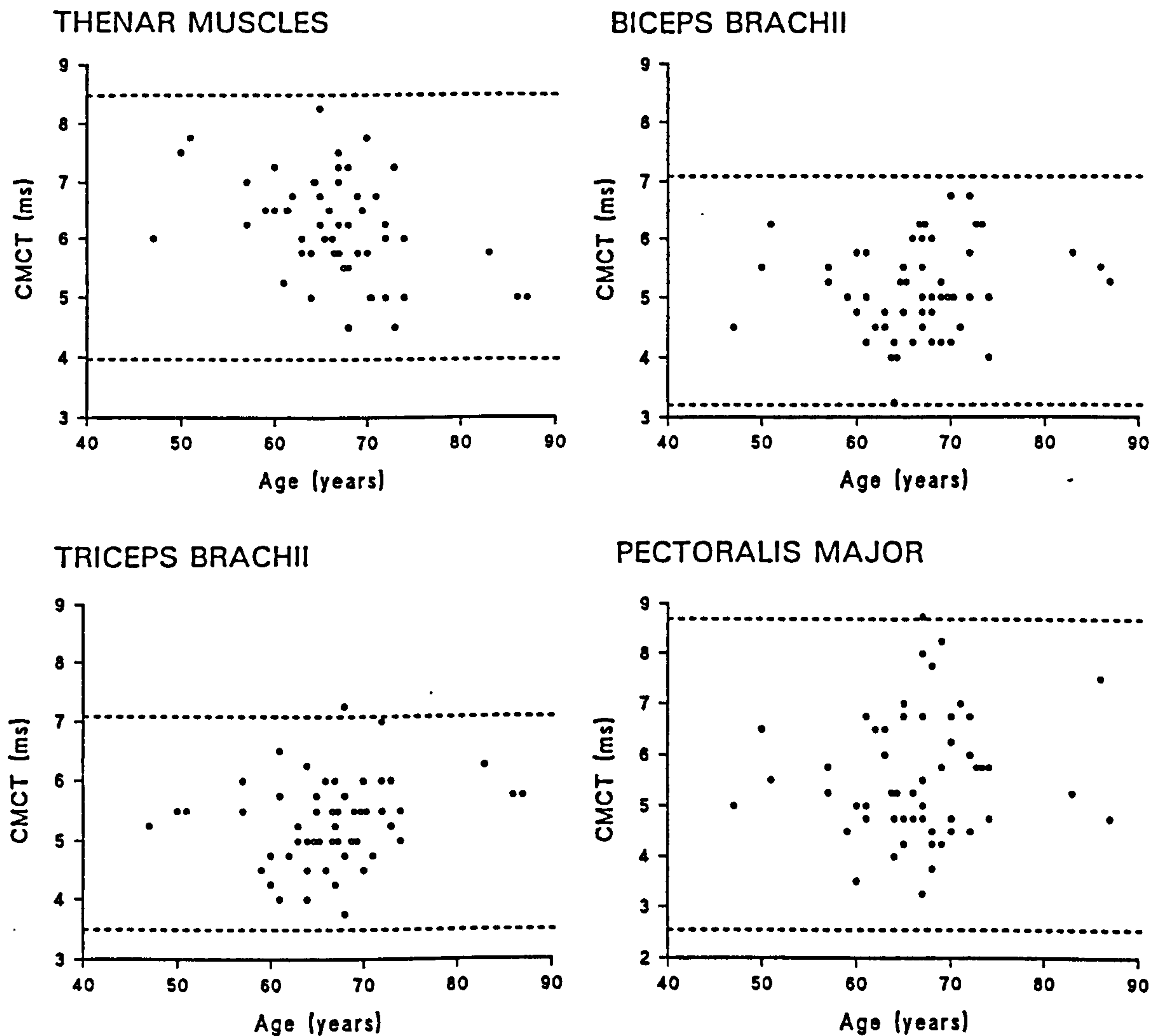


Figure 6. Central motor conduction time (CMCT) with respect to age in normal subjects. The values were obtained from 53 healthy subjects from recordings in the thenar muscle, biceps brachii, triceps brachii and the pectoralis major muscles. The broken lines indicate the 99% confidence interval.

MUSCLE	CMCT (ms)	DURATION (ms)
Thenar	6.2 \pm 0.9	41.6 \pm 6.8
Biceps brachii	5.1 \pm 0.8	40.9 \pm 7.5
Triceps brachii	5.3 \pm 0.7	39.1 \pm 7.2
Pectoralis major	5.6 \pm 1.2	42.3 \pm 10.5

Table 11. Central motor conduction values for CMCT and duration of response (mean \pm S.D.) for normal subjects.

Threshold to stimulation

The mean thresholds of the responses to motor cortex stimulation in relaxed biceps brachii and thenar muscles are shown in Table 12. The threshold to stimulation of the thenar muscles in the hand was slightly lower than the level for biceps brachii. The values for left and right hemispheres do not differ significantly and the values given are the average for the two hemispheres. Therefore using the results from normal subjects the normal range for threshold was regarded as the mean \pm 2.58 S.D. i.e. the 99% confidence interval. Any values for stroke patients that lie outside the normal range were regarded as abnormal.

MUSCLE	THRESHOLD - POWER %
Thenar	32.7 \pm 13.2
Biceps brachii	36.7 \pm 12.3
Triceps brachii	-
Pectoralis major	-

Table 12. Threshold to stimulation expressed as power (mean \pm S.D.) for normal subjects.

3.3 STROKE PATIENTS

Timing of the first investigations after stroke

All the patients had their first set of investigations completed within 12-72 hours of the onset of symptoms (Day 1) with a median value of 47.5 hours (mean \pm S.D. = 44.8 ± 17.1).

Exclusions prior to entry to study

Of 327 patients, approached and reviewed in the selection procedure, 206 patients were not recruited for the reasons given in Table 13A.

Exclusions following entry to study

In addition to the 118 first-ever stroke patients in the study a further three patients were originally recruited. All three patients met the inclusion criteria and appeared to have sustained a stroke. In each case a confident clinical diagnosis of stroke was made. However, they were excluded after entry when the CT scans revealed other types of pathology (Table 13B). CT scanning identified a subarachnoid haemorrhage in one patient and bilateral subdural haematomas in another. Multiple areas of infarction with an unusual appearance and widespread patchy distribution were observed in the third case. The case notes from another hospital of the third case revealed previous neurological disease in the form of sarcoidosis. The results from these patients were excluded from the study.

EXCLUSIONS TO STUDY	(n = 206)
Wrong diagnosis	24
Previous stroke	58
Neurological disease / head injury	13
Moribund or died prior to EMS	30
History of epileptic fit	13
Unstable atlanto-axial joint	4
Pacemaker	2
Metal in face or eyes ¹	1
No consent given	29
Too ill to travel or transport problems	15
Fractured humerus	1
Outside the 72 hours inclusion period	16

Table 13A. Reasons for excluding 206 patients from the study.

¹ Five patients excluded for other reasons given above, were also aware of the presence of metal fragments in the face or eyes as a result of shrapnel injury or occupational damage. Hence it is very important to enquire about metal in the head before embarking upon the use of EMS of the brain in any patient.

EXCLUSIONS AFTER ENTRY INTO STUDY (n = 3)	
Reason for exclusion	Number of patients
Subarachnoid haemorrhage	1
Subdural haematoma	1
Neurosarcoidosis	1

Table 13B. Reasons for the exclusion of three patients after entry into study.

Patient compliance

All 118 patients were followed to the completion of the study (12 or 18 months) or to death if this occurred earlier. The neurophysiological assessment at 12 months was not completed in eight of the 76 survivors. Two patients had left the region, therefore excluding assessments of neurophysiological testing, examination of tone and reflexes, the Nine-hole Peg Test and the Motricity Index. One patient was moribund. Three patients declined further neurophysiological testing. Two patients developed seizures not related to EMS. With these exceptions the final assessment of all survivors at 12 months was complete (Table 14).

Handedness and side of weakness after stroke

The details regarding hemispheric dominance and which side was affected by stroke are given in Table 15. The presence or absence of responses following cortical stimulation, CMCT, duration of response or threshold to stimulation was not related to the affected hemisphere whether dominant or non-dominant.

REASONS FOR INCOMPLETE NEUROPHYSIOLOGICAL STUDIES AT 12 MONTHS (n = 8)	
Reason for omission	Number of patients
Left region ¹	2
Moribund	1
Refused further tests	3
Epileptic seizure	2

Table 14. Reasons for failure to complete sequential neurophysiological investigations up to 12 months in eight patients.

¹ These two patients moved a considerable distance away from the region and although information regarding their functional abilities was obtained by telephoning their carers, no data for neurophysiological assessment, examination of tone and reflexes, the Nine-hole Peg Test and the Motricity Index was available at 12 months.

SIDE OF BODY	NUMBER OF PATIENTS (n = 118)	HANDEDNESS	
		left	right
Side of weakness:			
left	63 (53.4%)	2	61
right	53 (44.9%)	5	48
left + right	2 (1.7%)		2

Table 15. Handedness and paretic side of the body in stroke patients.

3.4 NEUROPHYSIOLOGICAL RESULTS AT DAY 1 IN STROKE PATIENTS

3.4.1 CMCT estimated from responses recorded in the paretic arm following EMS of the damaged hemisphere at Day 1

EMG responses to motor cervical root stimulation were always present but responses to motor cortex stimulation were more variable or absent. Responses in the muscles of the paretic side to contralateral cortical stimulation were only obtained in some patients with facilitation by contraction of the target muscle or the homologous muscle of the non-paretic side. The use of muscle contraction to facilitate responses to cortical stimulation was observed in all patients throughout the 12 months of follow-up after stroke. The facilitation of the responses to cortical stimulation is important, since 15 patients at Day 1 would otherwise have been categorised in the No Response Group with respect to the results from the thenar muscles and 19 patients in the No Response Group with respect to the results from biceps brachii. Comparable studies by other authors in this field have used a similarly powered electromagnetic stimulator, so that it is likely many false negative responses have been recorded. Table 16 demonstrates the number of patients in whom responses are present without muscle contraction and in those patients in whom responses are only present facilitated by muscle contraction. Since the thresholds were only measured for the thenar and biceps brachii muscles this observation only relates to these two muscles.

The mean values for CMCT and the duration of responses for the four target muscles of the paretic and non-paretic sides are given in Table 17.

RESPONSES IN PARETIC LIMB	NUMBER OF PATIENTS (n = 118)
Thenar muscles	
Obtained in relaxed muscle	59
Obtained in contracted muscle	15
No response despite contraction	44
Biceps brachii	
Obtained in relaxed muscle	53
Obtained in contracted muscle	19
No response despite contraction	46

Table 16. The presence of responses in the thenar and biceps brachii muscles for:

- 1) relaxed muscles.
- 2) only obtained in muscles with contraction of the target muscle or the homologous muscle on the non-paretic side.
- 3) muscles with no response even at 100% stimulus power with muscle contraction.

DAY 1	PARETIC SIDE		NON-PARETIC SIDE	
	CMCT (ms)	Duration (ms)	CMCT (ms)	Duration (ms)
Thenar	6.4 \pm 1.7	38.4 \pm 14.5	5.7 \pm 1.4	44.0 \pm 13.2
Biceps brachii	5.0 \pm 1.3	41.3 \pm 15.0	4.9 \pm 0.9	48.0 \pm 14.9
Triceps brachii	6.1 \pm 2.0	42.6 \pm 15.4	5.3 \pm 1.3	44.5 \pm 14.9
Pectoralis major	6.4 \pm 2.5	44.1 \pm 16.5	6.0 \pm 2.0	47.8 \pm 16.3

Table 17. Central motor conduction values (mean \pm S.D.) and duration of responses (mean \pm S.D.) in the muscles of the paretic and non-paretic upper limbs in stroke patients at Day 1.

At Day 1 following stroke three groups of patients were identified by measurement of CMCT, calculated by responses in the thenar muscles and by comparison of the values with those obtained from normal subjects. Patients either had **normal CMCT** values (within 99% confidence limits for normal subjects), **delayed CMCT** values (>99% confidence limits for normal subjects) or **no responses** (See: Figs. 5B, C and D, respectively). Hence patients are categorised into **Normal Response, Delayed Response and No Response Groups**. A similar grouping could be made using the CMCT values obtained for each muscle tested. At every time of testing during the study some patients could be assigned to each group. Table 18 shows the distribution of the categories with respect to the different muscles at Day 1.

The most prolonged CMCT of 29.0ms was recorded in biceps brachii at Day 28. This value is considerably longer than the mean CMCT in normal subjects ($5.1\text{ms} \pm 0.77 \text{ S.D.}$). On the few occasions where CMCTs were short and below the normal range, they were regarded as normal, since the functional progress and outcome of this small group was the same as for those individuals whose CMCTs fell within the normal range.

Responses to cortical stimulation may be absent from a single target muscle in the paretic arm, but usually more than one muscle was observed to have lost responses. The number of patients with absent responses in the target muscles are shown in Table 19. 61 patients had recordable responses in all the muscles at Day 1 whereas 57 patients had no responses in one or more target muscles at Day 1. 32 patients had no responses in all the target muscles following cortical stimulation at Day 1.

TARGET MUSCLE	NORMAL ¹	DELAYED	NO RESPONSE
Thenar	67	7	44
Biceps brachii	67	5	46
Triceps brachii	53	14	51
Pectoralis major ²	56	11	45

Table 18. Number of patients in each CMCT group at Day 1 (n= 118).

¹ This contains two values for the thenar muscles and two values for triceps brachii which were below the 0.5% confidence limit of the normal range. These results were included in the Normal Response Group since the outcome of these patients was the same as patients with normal CMCT.

² Poor quality responses were recorded from pectoralis major in six patients at Day 1 and the results were discarded. Therefore n= 112 for pectoralis major.

NUMBER OF MUSCLES WITH NO RESPONSES AT DAY 1.	NUMBER OF PATIENTS (n = 118)
One muscle	6 (5.1%)
Two muscles	5 (4.2%)
Three muscles	14 (11.9%)
Four muscles	32 (27.1%)
Responses in all muscles	61 (51.7%)

Table 19. The number of muscles in which responses could not be obtained following cortical stimulation at Day 1. The number of patients is shown for each catagory.

3.4.2 CMCT and duration of the response in the non-paretic arm following EMS of the undamaged hemisphere at Day 1

Only two patients did not have responses in relaxed muscles of the non-paretic limb at 100% stimulation at Day 1. All patients had responses in the muscles of the non-paretic limb following stimulation of the undamaged hemisphere with the target muscles contracted. Responses could always be obtained following stimulation of the spinal motor roots. Values of CMCT and the duration of the responses obtained from the responses of muscles in the non-paretic arm following stimulation of the undamaged hemisphere were all within the normal range (See Table 17).

3.4.3 Threshold of responses following EMS of the damaged and non-damaged hemispheres at Day 1

The mean thresholds for evoking responses in biceps brachii and the thenar muscles in both the paretic and non-paretic limbs for all patients demonstrating responses in relaxed muscles at Day 1 are shown in Table 20. It should be noted that patients who did not have responses even at 100% stimulation are not included in the calculation of means, i.e. the thresholds are not regarded as zero %. Hence only the results of patients who demonstrated responses in relaxed muscles are included in the calculations. In keeping with the findings in normal individuals, the thresholds to cortical stimulation were lower for the thenar muscles in the hand compared to biceps brachii.

SUBJECTS	BICEPS BRACHII	THENAR MUSCLES
Normal subjects ¹	36.7 \pm 12.3	32.7 \pm 13.2
Stroke patients		
Day 1 responders ² :		
Paretic limb	51.3 \pm 20.8	47.4 \pm 20.0
Non-paretic limb	38.9 \pm 15.5	34.9 \pm 13.3
All stroke patients ³		
Non-paretic limb	41.9 \pm 17.5	38.1 \pm 15.6

Table 20. Thresholds of responses in relaxed biceps brachii and thenar muscles at Day 1 (mean \pm S.D.). The results for normal subjects are also given for comparison.

¹ n = 53.

² n = 53 for biceps brachii, n = 59 for thenar muscles.

³ n = 116. Responses were only obtained in two patients following EMS of the undamaged hemisphere when the target muscles were contracted.

3.5 CENTRAL MOTOR CONDUCTION IN THE FIRST 12 MONTHS AFTER STROKE

3.5.1 Changes in CMCT from responses recorded in the paretic arm during the first 12 months after stroke

The results of CMCT for all target muscles at each test from Day 1 to 12 months are shown in Fig. 7. The 12 months following stroke represent a period in which major changes occur in clinical signs and sensorimotor abilities. Sequential neurophysiological investigations also revealed marked changes in the CMCT. The changes observed were similar for all the muscles tested and included:

1. Responses may remain unchanged with normal CMCT, delayed CMCT or no response.
2. Patients with no responses may gain responses with either normal or delayed CMCT.
3. Delayed CMCT may become normal.
4. Responses may be lost if the stroke evolves.

The majority of patients with normal CMCT at Day 1 retained normal conduction throughout the 12 month period. 16 of the 44 patients with no responses in thenar muscles at Day 1 survived and were investigated at 12 months (See: 3.3 Stroke patients - Patient compliance, for reasons why some of the survivors did not receive EMS). The majority of patients with no responses at Day 1 gain responses by 3 months, however the process takes longer in some patients.

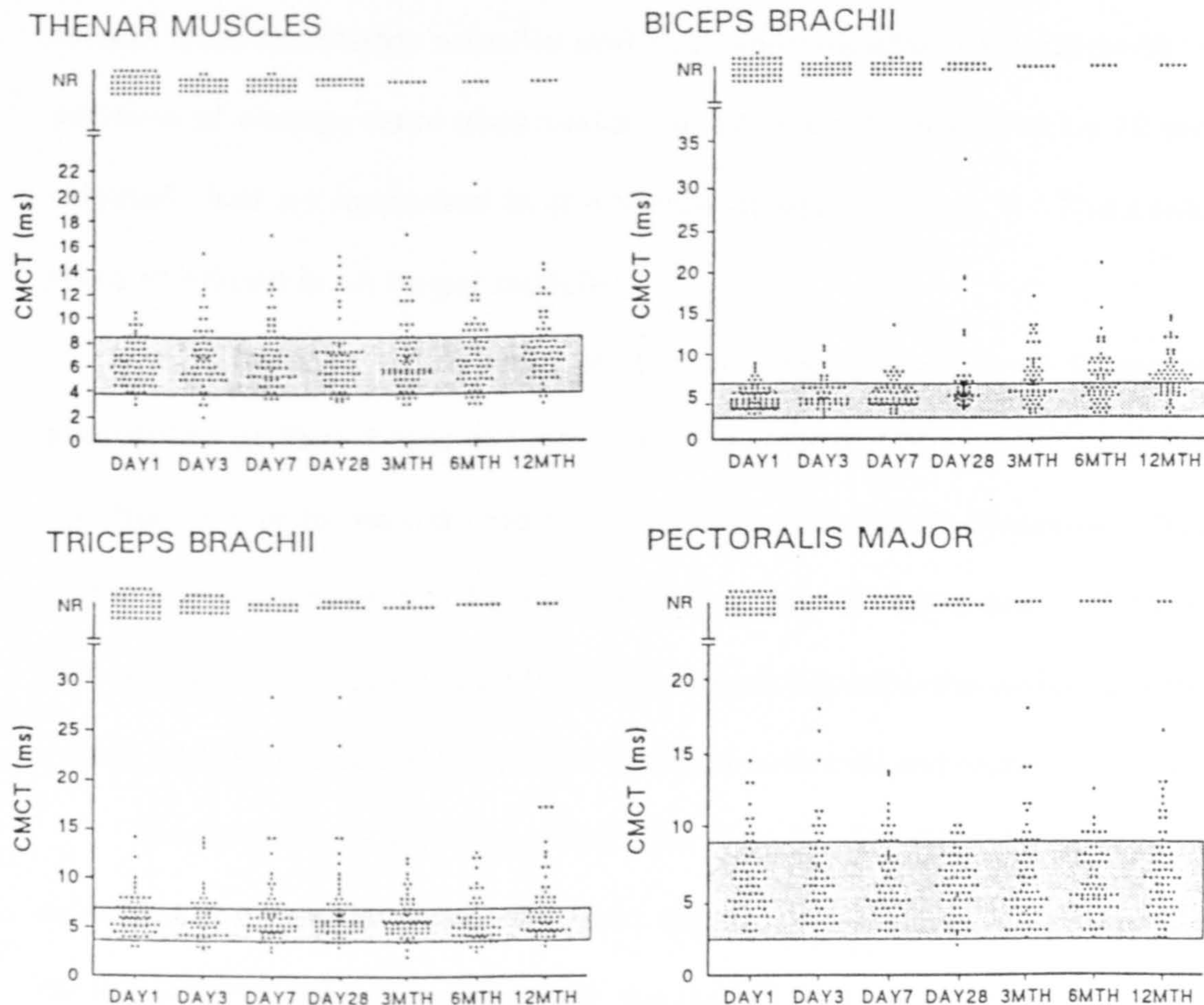


Figure 7. Central motor conduction time (CMCT) for thenar, biceps brachii, triceps brachii and pectoralis major muscles at each test session following stroke. The values for each stroke patient are shown individually. Measurements were made on 118 patients at Day 1 and the subsequent reduction in numbers result from the 42 deaths during the study. The stippled areas indicate the normal range (99% confidence interval) for each muscle. MTH, month.

Three patterns of change were observed. Responses remained absent ($n = 4$), responses returned by 12 months with delayed CMCT ($n = 7$), or responses returned with normal CMCT ($n = 5$). These patterns are illustrated in Fig. 8 using results from the thenar muscles and five representative case histories. The same patterns of change were observed in the 24 patients who died by 12 months who originally had no responses in the thenar muscles at Day 1. The same changes were observed in all target muscles.

The number of patients in the No Response Group following cortical stimulation at Day 1 had reduced considerably at 12 months. The reduction in numbers is due to the high mortality of patients in the No Response Group. Most of the survivors from the No Response Group gain responses. Of the responses that appear most have delayed CMCTs, which explains the wider spread of CMCT values and the increased number of patients with delayed responses at 12 months.

Some patients lost responses after Day 1. On clinical grounds 14 patients extended their stroke during the first seven days after entry to the study. The clinical deterioration coincided with the loss of responses in some target muscles even though responses had been observed previously at Day 1.

Table 21 compares the distribution of the three response groups with respect to the different muscles at Day 1 and at 12 months. The reduction in numbers of patients tested at 12 months was due to the death of 42 patients and a further eight patients who could not be tested (See: 3.3 Stroke patients - Patient compliance). Although observations were made on four different muscles, the responses in the thenar muscles have been taken as the most representative and the best link to the clinical assessments.

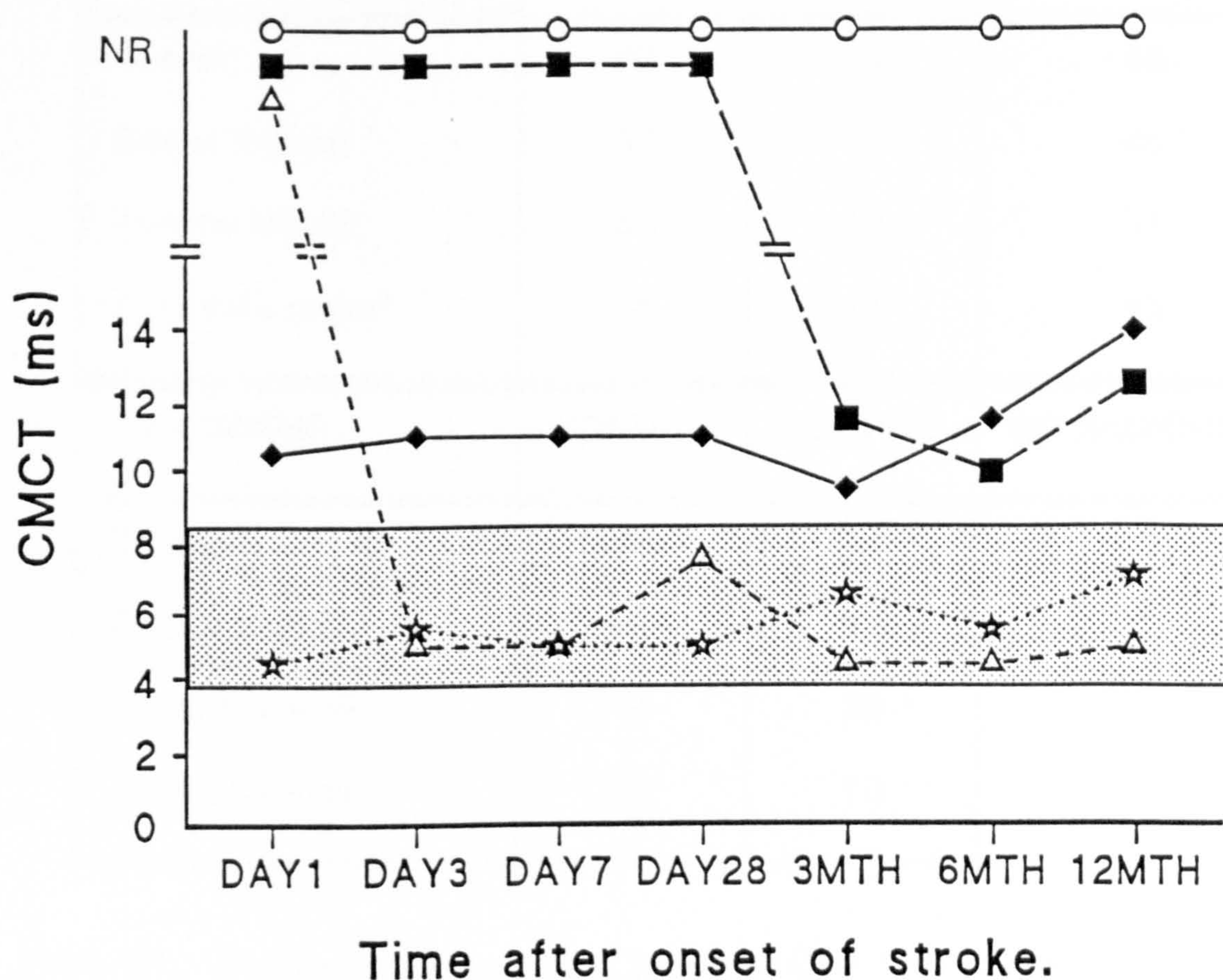


Figure 8. Patterns of change in central motor conduction time (CMCT) illustrated by data from five stroke patients obtained from recordings in thenar muscles.

- no response to cortical stimulation throughout the study.
- initially no response, but delayed CMCT appearing at three months.
- ◆ delayed central motor conduction throughout the study.
- △ initially no response, but normal central motor conduction in first week following stroke and maintained throughout the study.
- ☆ normal central motor conduction throughout the study.

Stippled areas indicate normal range (99% confidence interval).

DAY 1	NORMAL ¹	DELAYED	NO RESPONSE
Thenar	67	7	44
Biceps brachii	67	5	46
Triceps brachii	53	14	51
Pectoralis major ²	56	11	45
12 MONTHS	NORMAL ¹	DELAYED	NO RESPONSE ³
Thenar	49	14	5
Biceps brachii	52	13	3
Triceps brachii	44	20	4
Pectoralis major	52	13	3

Table 21. Number in each patient group at Day 1 (n=118) and for survivors studied at 12 months (n=68).

¹ This also contains two sets of values for the thenar muscles and two sets of values for triceps brachii which fell below the 0.5% confidence limit of the normal range. Where CMCTs were short and below the normal range, they were regarded as normal, since the functional progress and outcome of this small group proved to be the same as for those individuals whose CMCTs fell within the normal range.

² Poor quality responses recorded from pectoralis major in 6 patients lead to the results being discarded, therefore n=112.

³ Included patients in whom absent responses did not return and patients whose stroke extended causing subsequent loss of responses that did not return.

The variation in the different conduction groups, in particular the greater number and spread of CMCTs in patients with delayed conduction, accounts for the greater value of the mean CMCTs for the patients tested at 12 months. The Day 1 CMCT values are compared to the CMCTs at 12 months in (Table 22).

From this point onwards in the thesis any reference to central motor conduction results will refer to those obtained from recordings taken in the thenar muscles (unless other muscles are specifically named). The principles apply to all the target muscles. The results from the thenar muscles have been chosen since they represent the best observation of how neurophysiological changes relate to clinical state and the recovery of motor function.

3.5.2 Evolution and severity of stroke

Stroke often evolves over a period of days, and although some physical signs rapidly become established it is often a few days before the neurological damage is complete. A second group of patients has therefore been defined with no response following cortical stimulation on one or more occasions on Days 1-7. The two patient groups of no responders are:

- 1) Patients with no response to cortical stimulation at Day 1 (The No Response Group).
- 2) Patients with no response to cortical stimulation on one or more occasions at Day 1, Day 3 or at Day 7 (Days 1-7).

These groupings can be used to refer to the results from one target muscles or to the absence of responses from one or more target muscle.

DAY 1	PARETIC SIDE		NON-PARETIC SIDE	
	CMCT (ms)	Duration (ms)	CMCT (ms)	Duration (ms)
Thenar	6.4 \pm 1.7	38.4 \pm 14.5	5.7 \pm 1.4	44.0 \pm 13.2
Biceps brachii	5.0 \pm 1.3	41.3 \pm 15.0	4.9 \pm 0.9	48.0 \pm 14.9
Triceps brachii	6.1 \pm 2.0	42.6 \pm 15.4	5.3 \pm 1.3	44.5 \pm 14.9
Pectoralis major	6.4 \pm 2.5	44.1 \pm 16.5	6.0 \pm 2.0	47.8 \pm 16.3

12 MONTHS	PARETIC SIDE		NON-PARETIC SIDE	
	CMCT (ms)	Duration (ms)	CMCT (ms)	Duration (ms)
Thenar	7.4 \pm 2.4	44.7 \pm 15.7	6.0 \pm 1.3	43.1 \pm 12.6
Biceps brachii	6.2 \pm 2.4	43.1 \pm 13.4	5.1 \pm 0.7	45.9 \pm 12.4
Triceps brachii	6.9 \pm 3.1	43.3 \pm 14.4	5.3 \pm 1.2	46.4 \pm 12.6
Pectoralis major	6.8 \pm 2.9	50.6 \pm 17.7	5.9 \pm 1.9	49.7 \pm 16.6

Table 22. Central motor conduction values (mean \pm SD) in paretic and non-paretic sides in stroke patients at Day 1 and at 12 months.

Regrouping the patients with no responses on one or more occasions on Days 1-7 includes patients whose stroke has progressed and who have subsequently lost responses. The reason for making this additional group is that the results suggest that absent responses are of great prognostic importance. Hence the absence of responses in any muscle on one or more occasions in any of the first three test sessions (Days 1-7) merits further consideration.

3.5.3 Changes in the duration of responses recorded in the paretic arm during the first 12 months after stroke

The mean values for duration of the responses following cortical stimulation obtained in all muscles of both the paretic and non-paretic sides in the stroke patients at any test session were not significantly different from the normal subjects (Table 22). However, the duration of responses that reappeared in the patients with no responses on Days 1-7 were shorter for thenar muscles ($p=0.007$), biceps brachii ($p=0.01$) and pectoralis major ($p=0.04$) than in those patients who had not lost responses on Days 1-7. The results for triceps were not significant ($p>0.05$). (All tests used the Mann-Whitney U test)

3.5.4 Threshold to electromagnetic stimulation of the motor cortex after stroke

The thresholds to cortical stimulation were only assessed in the relaxed biceps brachii and thenar muscles (See: 3.1 Pilot cross-sectional study). Table 23 compares the thresholds for normal subjects with different groups of patients at

NORMAL SUBJECTS

	BICEPS BRACHII	THENAR MUSCLES
	36.7 ± 12.3	32.7 ± 13.2

STROKE PATIENTS. DAY 1 RESPONDERS (Normal and Delayed Response Groups).

SIDE OF BODY	BICEPS BRACHII			THENAR MUSCLES		
	Day 1	Month 12	p value	Day 1	Month 12	p value
Paretic	51.3	29.6	*	47.4	30.4	*
Non-paretic	38.9	28.4	*	34.9	26.1	*

ALL STROKE PATIENTS.

SIDE OF BODY	BICEPS BRACHII			THENAR MUSCLES		
	Day 1	Month 12	p value	Day 1	Month 12	p value
Non-paretic	41.9	29.4	*	38.1	27.3	*

Table 23. Thresholds of responses in relaxed biceps brachii and thenar muscles expressed as % of maximal power output. The results for individuals at Day 1 are compared to the corresponding values for the same surviving patients at 12 months. * = p <0.0001. (Wilcoxon matched pairs signed rank test).

Day 1 and at 12 months. In normal subjects the mean threshold for biceps brachii was 36.7% of maximum power output and for thenar muscles 32.7%. For all patients with responses at Day 1 (Normal and Delayed Groups), who continued to demonstrate responses at subsequent test dates, the means at Day 1 were 51.3% for biceps brachii and 47.4% for thenar muscles; they decreased to 29.6% and 30.4%, respectively, at 12 months. The threshold values for patients with responses although starting at levels significantly above normal values decreased over 12 months to values that were significantly lower than normal values.

The group of patients without responses (No Response Group) did not have recordable thresholds at Day 1 and, upon gaining responses, invariably did so at maximum stimulus power (100%). To include the values for this group of patients in any calculation of threshold value would lead to an overestimation and skew the mean value for the entire group investigated at 12 months. This would effectively obscure the changes in thresholds for the patients with responses at Day 1. Therefore, the threshold values of patients who gained responses have been omitted from the calculation of mean values of threshold for the responses recorded in the paretic limb.

In the patients who had responses at Day 1 on the paretic side, a similar decrease in threshold was also observed in muscles of the non-paretic side (Table 23). The threshold for muscles on the non-paretic side also fell for the entire group of patients, whether responses could be recorded or not at Day 1 in muscles of the paretic side. The reduction in threshold from Day 1 to 12 months was significant for values obtained from both the damaged or undamaged hemispheres.

3.6 SAFETY OF ELECTROMAGNETIC STIMULATION FOLLOWING STROKE

Symptoms following EMS of the brain

No complications occurred during, or directly following the use of EMS. No healthy volunteer or stroke patient, even those with very extensive areas of brain damage complained of any symptoms. This was despite the fact that sequential investigations were repeated over many months, often using the maximum power output of the stimulator. A few patients did comment upon the loud click that the coil produces during the emission of the magnetic field. The small number of patients who declined further neurophysiological tests after commencing the study, did not do so because of adverse effects from the test.

Incidence of epileptic seizures

Only 2 (1.7%) patients experienced a seizure during the whole project. In both cases this did not occur for more than four weeks after EMS. No seizures were observed at the time of cortical stimulation.

3.7 RADIOLOGICAL AND CLINICAL ASSESSMENTS AFTER STROKE

3.7.1 CT scanning after stroke

Three of the 121 patients originally entered into the study were excluded after entry when other pathology was identified on CT scans. 118 patients remained in the study and 107 patients received scans, all of which had features compatible with stroke (Table 24). Three of the 11 patients who were not scanned were examined at autopsy and had evidence of stroke. Therefore, 110 patients had additional radiological or pathological evidence to support the clinical diagnosis of stroke.

100 patients were scanned within 14 days of onset of symptoms, four were scanned between 15 and 30 days and three after 30 days. The median time to scanning was 6 days (mean = 9.0 days \pm 12.0 S.D.). 85 of the 107 scans of patients identified lesions compatible with stroke. There were 17 patients with haemorrhage, 68 with infarction, of which six had signs of haemorrhagic infarction. A further 22 patients had a normal CT scan. The mean horizontal diameter of the lesions was 58.1 \pm 35.0 mm, the mean approximate spherical volume was 66,287 \pm 76,472 mm³. Approximately half the lesions seen had mass effect. More lesions were seen in the right hemisphere. In most cases the lesions were confluent. Most lesions involved cortical and subcortical structures. Damage to subcortical structures alone was seen on 32 scans, but only three scans demonstrated purely cortical lesions. The most consistent arterial territory causing stroke was the middle cerebral artery.

CT FEATURE		NUMBER OF PATIENTS (n = 107)
Haemorrhage		17
Infarction ¹		68
Normal		22
Horizontal diameter mm (mean)		58.1 \pm 35.0
Volume mm ³ (mean)		66287.0 \pm 76472
Ventricular rupture		3
Hydrocephalus		0
Mass effect ²		42
Site:	Cortical	3
	Subcortical	32
	Cortical + subcortical	50
Laterality of lesion:	Left	32
	Right	50
	Midline	0
	Left + Right	3
Pattern of lesion:	Confluent	74
	Patchy	11
Arterial territory:		
Posterior inferior cerebellar artery	(PICA)	0
Basilar artery	(BA)	1
Anterior inferior cerebellar artery	(AICA)	0
Superior cerebellar artery	(SPA)	0
Posterior cerebral artery	(PCA)	12
Anterior choroidal artery	(AChA)	7
Anterior cerebral artery	(ACA)	7
Middle cerebral artery	(MCA)	66
Perforating lenticulostriate arteries	(PLA)	5
More than one territory involved		13

Table 24. Neuroradiological features identified on CT scans.

¹ Includes 6 patients with infarction plus haemorrhage.

² 85 patients had visible lesions, 42 had mass effect, 42 had no mass effect and in one patient the opinion of the clinicians who reported the scans was divided.

The relationship of CT scan features to central motor conduction

No correlation to CMCT was found for ventricular rupture, hydrocephalus, laterality or pattern of lesion and arterial territory. Correlations with CMCT were found for type of stroke, horizontal diameter, volume of lesion, mass effect and site of lesion. The results of the CT scan features and the relationship to central motor conduction are shown in Tables 25 and 26.

When haemorrhage and infarction were compared with the presence or absence of responses on Days 1-7, a larger proportion of patients with infarction had no responses to cortical stimulation (54.4%). Patients with infarction accounted for the majority of those with no response following EMS. Only 23.5% of patients with haemorrhage had no responses. Most patients with normal scans retained cortical responses, however, five patients out of 22 (22.7%) with a normal scan had absent responses.

The size of the lesion was important in terms of the largest single diameter on any CT scan view and the approximate spherical volume. The larger the lesion the greater the probability of no responses following cortical stimulation.

The relationship of absent responses in the presence of mass effect was the least clear. The majority of patients with no response on Days 1-7 (62.5%) have evidence of mass effect on their scans. However 15 patients with no visible mass effect from the lesion also had no responses following EMS.

Lesions involving the cortex were more likely to be associated with absent responses. 64% of patients with cortical lesions lost responses, whereas only 22% of patients with purely subcortical lesions had no responses following EMS.

CT SCAN FEATURE		PATIENTS WITH RESPONSES PRESENT (n=61)		PATIENTS WITH NO RESPONSE (n=46)	
		Day 1	Days 1-7	Day 1	Days 1-7
Haemorrhage	(n=17)	14	13	3	4
Infarction	(n=68)	37	31	31	37
Normal scan	(n=22)	17	17	5	5
Horizontal diameter ¹	(mean)	44.9	39.9	78.7	78.2
Spherical volume ²	(mean)	35,253	25,617	112,837	109,932
Mass effect ³	(n=42)	22	17	20	25
No mass effect	(n=42)	29	27	13	15
Cortical lesion	(n= 3)	2	2	1	1
Subcortical lesion	(n=32)	26	25	6	7
Cortical + subcortical	(n=50)	23	17	27	33

Table 25. The most important CT scan features and their relationship to central motor conduction. The patients are subdivided on the basis of having no response on Day 1 or no response on one or more occasions on Days 1-7. The central motor conduction results pooled for Days 1-7 are more representative than Day 1 results in view of the fact that the CT scans were performed at various times after the onset of stroke and hence did not correspond to a particular test day.

¹ Horizontal diameter in mm.

² Spherical volume in mm³.

³ n=84 for the presence or not of mass effect. The scan of one patient was regarded as "not sure" by the three clinicians who interpreted the scans.

CT SCAN FEATURE	CORRELATION WITH ABSENCE OF RESPONSES	
	Day 1	Days 1-7
Type of stroke	$p < 0.05$	$p < 0.05$
Horizontal diameter	$p = 0.001$	$p < 0.0001$
Spherical volume	$p = 0.0001$	$p < 0.0001$
Mass effect	NS	$p < 0.05$
Site	$p < 0.005$	$p < 0.0005$

Table 26. The following scan features correlated with loss of responses on Day 1 and on Days 1-7 after stroke:

1. Infarction was more likely to be present if responses were absent (Chi-Square).
2. The larger the horizontal diameter or spherical volume of the lesion the greater the probability of no response to cortical stimulation (Mann-Whitney U test).
3. Response were likely to be absent if mass effect was present (Chi-Square).
4. Purely subcortical lesions were more likely to lead to loss of responses compared to lesions that included the cortex (Chi-Square).

No correlation was found between delayed CMCT and CT scan appearances. Of the seven patients with delayed responses in the thenar muscles on Day 1, one patient had a normal scan, six patients had visible lesions of which five had mass effect. In two patients the lesions were purely subcortical but in the other four scans both the cortex and subcortex were involved.

3.7.2 Symptoms after stroke

The neurological symptoms reported by patients between the onset of stroke to the first assessment at Day 1 are recorded in Table 27. Awareness of upper limb weakness was a common feature. Although not all patients were initially aware of weakness in the limbs, all 118 patients in the study demonstrated signs of motor weakness at Day 1. Sensory symptoms in the limbs were less common.

The relationship of symptoms with central motor conduction

Symptoms at the onset of stroke that correlated with no response in a target muscle at any time on Days 1-7 are shown in Table 28 (applies to all four target muscles). A correlation with absent responses in the target muscles was found to exist for the presence of weakness in hand, arm or leg on the paretic side of the body ($p < 0.05$); swallowing problems ($p < 0.05$); visual problems ($p < 0.05$); and the loss of urinary continence ($p < 0.005$). No relationship was found for the following symptoms: speech problems; facial weakness; loss of consciousness at onset of stroke; headache; sensory disturbance; loss of bowel continence.

SYMPTOM DUE TO STROKE	NUMBER OF PATIENTS (n = 118)	
Speech problem ¹	72	(61.0%)
Swallowing problem	37	(31.4%)
Weakness of facial muscles:		
Left side	26	(22.0%)
Right side	24	(20.3%)
Both sides	0	
Weakness of hand muscles:		
Left side	60	(50.8%)
Right side	39	(33.1%)
Both sides	1	(0.8%)
Weakness of arm muscles:		
Left side	60	(50.8%)
Right side	37	(31.4%)
Both sides	1	(0.8%)
Weakness of leg muscles:		
Left side	45	(38.1%)
Right side	28	(23.7%)
Both sides	4	(3.4%)
Loss of consciousness	16	(13.6%)
Visual disturbance	25	(21.2%)
Headache	40	(33.9%)
Sensory disturbance:		
Left side	27	(22.9%)
Right side	22	(18.6%)
Both sides	2	(1.7%)
Loss of urinary continence	28	(23.7%)
Loss of bowel continence	4	(3.4%)

Table 27. Number of patients who reported neurological symptoms at Day 1.

¹ Speech problems refers to any difficulty with speech encountered by the patient and thus includes dysarthria, dysphasia and dysphonia.

SYMPTOM	STATISTICAL SIGNIFICANCE
Weakness in hand, arm or leg on the paretic side of the body.	$p < 0.05$
Swallowing problems.	$p < 0.05$
Visual problems.	$p < 0.05$
Loss of urinary continence ¹ .	$p < 0.005$

Table 28. The relationship of symptoms to absence of responses following cortical stimulation. The results apply to all the target muscles demonstrating no responses on one or more occasions on Days 1-7 after stroke. (Chi-square with Yates correction when appropriate).

¹ No correlation existed for absence of responses observed in biceps brachii.

3.7.3 The Bamford clinical classification of stroke

The examination findings at Day 1 were used to allocate patients into four different clinical categories using the Bamford classification (Table 29A). The commonest clinical presentation was a lacunar syndrome (LACS). Slightly less than one third of patients had a total anterior circulation syndrome (TACS), and the same number had a partial anterior circulation syndrome (PACS). Only two patients were categorised as having a posterior circulation syndrome (POCS). Two patients could not be categorised to a particular group with certainty.

The relationship of the Bamford classification of stroke with central motor conduction

The relationship of the Bamford classification to central motor conduction is shown in Table 29B. 56.8% of patients with TACS had no responses in the thenar muscles at Day 1, compared to 46% of PACS and 15% of LACS. 43.2% of TACS and 54.1% of PACS had responses (Normal and Delayed Groups combined) following EMS compared to 85% of LACS. Patients with TACS were by definition, those with extensive hemispheric damage and a wide spectrum of clinical signs. Patients with TACS were the most likely to have no response following cortical stimulation. Only a small proportion of patients with LACS had no responses following cortical stimulation. When patients in the different Bamford categories with responses (Delayed or normal) were compared to patients without responses a correlation was found ($p = 0.007$, Chi-Sq) (Table 29B).

BAMFORD CLASSIFICATION	NUMBER OF PATIENTS (n= 118)
TACS	37 (31.4%)
PACS	37 (31.4%)
POCS	2 (1.7%)
LACS	40 (33.9%)
Unclassifiable	2 (1.7%)

Table 29A. The number of patients in each catagory as defined by the Bamford classification (Bamford et al., 1991).

- TACS total anterior circulation syndrome.
- PACS partial anterior circulation syndrome.
- POCS posterior circulation syndrome.
- LACS lacunar syndrome.

RESPONSES	TACS	PACS	POCS	LACS
No response	21	17	-	6
Normal	14	18	2	32
Delayed	2	2	-	2

Table 29B. Patients (n= 116) subdivided into the different Bamford categories. Different response groups (thenar muscles) at Day 1 are shown. When the group patients with responses (Delayed or normal) were compared to patients without responses in the different subgroups a correlation was present (p = 0.007, Chi-Sq)

3.7.4 Muscle tone and tendon reflexes after stroke

Examination of muscle tone and tendon reflexes at Day 1

At Day 1 all patients had evidence of changes in muscle tone and tendon reflexes. In some patients the abnormalities were not restricted to just the paretic side but were present on the non-paretic side. Presumably this was due to a number of factors affecting the undamaged hemisphere such as oedema, altered haemodynamics, mass effect and possibly secondary ischaemic damage. The changes in tone and tendon reflexes in the upper and lower limbs observed at Day 1 are given in Table 30. One patient had an above-knee amputation on the paretic side of the body and therefore it was not possible to assess changes in tone in the muscles acting about the knee or ankle, their associated reflexes or the plantar responses.

Examination of muscle tone at 12 months after stroke

The number and proportion of patients who demonstrated alterations of muscle tone at 12 months are shown in Table 31 (the two patients who left the Region were not assessed at 12 months). A considerably smaller number of patients demonstrated abnormal muscle tone at 12 months. This was partly due the resolution of abnormal tone and due to reduced patient numbers at 12 months due to the death.

ABNORMAL TONE	NUMBER OF PATIENTS (n = 118)
Upper limbs	102 (86.4%)
Lower limbs	72 (61.5%)
ABNORMAL TENDON REFLEXES	NUMBER OF PATIENTS (n = 118)
Biceps reflex	83 (70.3%)
Triceps reflex	57 (48.3%)
Supinator reflex	79 (66.9%)
Knee reflex	75 (64.1%)
Ankle reflex	51 (43.6%)
Extensor plantar response	102 (87.2%)

Table 30. The number of patients with clinical evidence of abnormal tone (either increased or decreased) in limbs of the paretic side of the body at Day 1. The lower part of the table also shows the number of patients with abnormal tendon reflexes (exaggerated or absent) and extensor plantar responses on the paretic side of the body at Day 1.

TONE AT DAY 1

ABNORMAL TONE	NUMBER OF PATIENTS (n = 118)	PATIENTS WITH NO RESPONSES (n = 53)	PATIENTS WITH RESPONSES (n = 65)
Upper limbs	102 (86.4%)	51	51
Lower limbs	72 (61.5%)	43	29

NORMAL TONE	NUMBER OF PATIENTS (n = 118)	PATIENTS WITH NO RESPONSES (n = 53)	PATIENTS WITH RESPONSES (n = 65)
Upper limbs	16 (13.6%)	2	14
Lower limbs	45 (38.5%)	9	36

TONE AT 12 MONTHS

ABNORMAL TONE	NUMBER OF PATIENTS (n = 74)	SURVIVORS WITH NO RESPONSES AT DAY 1 (n = 20)	SURVIVORS WITH RESPONSES AT DAY 1 (n = 52)
Upper limbs	29 (39.2%)	18	11
Lower limbs	24 (32.4%)	16	8

NORMAL TONE	NUMBER OF PATIENTS (n = 74)	SURVIVORS WITH NO RESPONSES AT DAY 1 (n = 20)	SURVIVORS WITH RESPONSES AT DAY 1 (n = 52)
Upper limbs	45 (60.8%)	4	41
Lower limbs	50 (67.6%)	6	44

Table 31. Changes in tone in the upper and lower limbs of the paretic side of the body at Day 1 and for the survivors at 12 months. The number of patients with responses or absence of responses following cortical stimulation are shown.

The relationship of muscle tone with central motor conduction

Following cortical stimulation the absence of responses in any of the target muscles on one or more occasions on Days 1-7, correlated with abnormalities in muscle tone (increased or decreased) in the arm ($p < 0.05$) and leg ($p = 0.0001$) on the paretic side of the body at Day 1. At 12 months 29 patients had abnormal tone in the upper limbs and 24 in the lower limbs on the paretic side of the body. The absence of responses following cortical stimulation after stroke on Days 1-7 correlated with abnormal tone in the arm ($p < 0.0001$) and in the leg ($p < 0.0001$) at 12 months. Patients with no responses in a target muscle at any time on Days 1-7 were more likely to demonstrate abnormal changes in tone, in both the upper and lower limbs on the paretic side at 12 months. Most patients with responses at Day 1 had normal tone at 12 months. The correlations between absence of responses and abnormal tone are shown in Table 32.

Examination of tendon reflexes at 12 months after stroke

The number of patients with abnormal tendon reflexes and plantar responses at 12 months was less than Day 1. This was due to clinical improvement and reduced number of patients due to death. Table 33 shows the number of patients with abnormal reflexes on the paretic side of the body at Day 1 and 12 months compared to the presence of responses (the two patients who left the Region were not assessed at 12 months). At both Day 1 and 12 months there are almost equal numbers of patients with or without responses who had abnormal reflexes.

ABNORMAL TONE	STATISTICAL SIGNIFICANCE
Days 1-7 In the paretic arm In the paretic leg	 $p < 0.05$ $p = 0.0001$
At 12 months In the paretic arm In the paretic leg	 $p < 0.0001$ $p < 0.0001$

Table 32. The absence of responses following cortical stimulation in any of the target muscles after stroke on any occasion on Days 1-7, correlated with abnormal muscle tone (Chi-Sq).

REFLEXES AT DAY 1

ABNORMAL REFLEXES	NUMBER OF PATIENTS (n = 118)	PATIENTS WITH NO RESPONSES (n = 53)	PATIENTS WITH RESPONSES (n = 65)
Biceps reflex	83 (70.3%)	39	44
Triceps reflex	57 (48.3%)	31	26
Supinator reflex	79 (67.0%)	34	45
Knee reflex	75 (63.6%)	35	40
Ankle reflex	51 (43.2%)	27	24
Plantar response	102 (86.4%)	50	52

REFLEXES AT 12 MONTHS

ABNORMAL REFLEXES	NUMBER OF PATIENTS (n = 74)	SURVIVORS WITH NO RESPONSES AT DAY 1 (n = 20)	SURVIVORS WITH RESPONSES AT DAY 1 (n = 52)
Biceps reflex	42 (56.8%)	19	23
Triceps reflex	29 (39.2%)	15	14
Supinator reflex	44 (59.5%)	20	24
Knee reflex	44 (59.5%)	20	24
Ankle reflex	23 (31.1%)	12	11
Plantar response	50 (67.6%)	20	30

Table 33. Abnormal reflexes in the upper and lower limbs on the paretic side of the body at Day 1 and for the survivors at 12 months. The number of patients with responses or absence of responses following cortical stimulation are shown.

The relationship of tendon reflexes with central motor conduction

There was no correlation between absent responses following cortical stimulation after stroke on Day 1 or Days 1-7 and tendon reflexes on the paretic side of the body at Day 1, or between absent responses on Day 1 and tendon reflexes at 12 months. However, abnormal tendon reflexes on the paretic side for survivors at 12 months did correlate with absent responses on Days 1-7 for all reflexes and for all the target muscles (all $p < 0.0001$) (Table 34). There was no correlation between absent responses at Day 1 and extensor plantar responses at Day 1. The absence of responses from any of the target muscles following cortical stimulation on any occasion on Days 1-7 correlated with an extensor plantar response on the paretic side at Day 1 ($p < 0.01$) and at 12 months ($p < 0.0001$).

3.7.5 The Motricity Index of muscle power after stroke

The Motricity Index at Day 1

Voluntary muscle strength was assessed by clinical examination and given weighted scores using the Motricity Index. There was a wide spectrum of scores at Day 1. All patients demonstrated some degree of motor impairment. Mild transient weakness was identified in the non-paretic limbs for some patients presumably due to bilateral damage and the factors mentioned above (See: 3.7.4 Muscle tone and tendon reflexes after stroke - Examination of muscle tone and tendon reflexes at Day 1). Apart from a few individuals with transient mild muscle weakness, muscle power on the non-paretic side fell within the normal range

ABNORMAL REFLEX	STATISTICAL SIGNIFICANCE
Day 1 Tendon reflexes in the paretic arm Tendon reflexes in the paretic leg (except ankle jerk) Ankle jerk Plantar response	NS NS $p < 0.01$ $p < 0.01$
At 12 months Tendon reflexes in the paretic arm Tendon reflexes in the paretic leg Plantar response	$p < 0.0001$ $p < 0.0001$ $p < 0.0001$

Table 34. The correlations between absence of responses following cortical stimulation in any of the target muscles after stroke on any occasion on Days 1-7 with abnormal tendon reflexes and plantar responses on the paretic side of the body at Day 1 and at 12 months (Chi-Sq).

irrespective of abnormalities of central motor conduction and the weakness of muscles on the paretic side. The mean scores for the paretic side are shown in Table 35.

The Motricity Index at 12 months after stroke

The mean scores for the Motricity Index for all survivors tested at 12 months are given in Table 36 (the two patients who left the region were not assessed at 12 months). The recovery of pinch grip, which is a movement with some contribution from the thenar muscles, was the movement that demonstrated the least recovery of power. On the whole, the return of power in the lower limb was better than in the upper limb. Most patients showed some improvement in muscle power of the paretic side at 12 months. Only a few patients achieved complete recovery of muscle power for all movements on the paretic side, most patients continuing to demonstrate weakness of some movements. A small number of patients remained completely paralysed in the upper limb with no improvement nor return of muscle power for certain movements. The slight reduction of power seen in some patients in the non-paretic side had completely resolved by 12 months with the exception of one rather frail patient.

MOTRICITY INDEX SCORES FOR PARETIC SIDE FOR ALL PATIENTS AT DAY 1 (n=118)	
Pinch grip	13.5 \pm 12.5
Elbow flexion	15.0 \pm 12.6
Shoulder abduction	14.6 \pm 13.0
Ankle dorsiflexion	17.2 \pm 14.1
Knee extension	19.8 \pm 12.7
Hip flexion	18.3 \pm 12.8
Upper limb total	43.9 \pm 36.9
Lower limb total	56.0 \pm 38.2
Side total	50.2 \pm 35.7

Table 35. The Motricity Index scores (mean \pm S.D.) for all 118 patients at Day 1.

MOTRICITY INDEX SCORES FOR PARETIC SIDE FOR PATIENTS AT 12 MONTHS (n = 74)	
Pinch grip	25.7 \pm 10.2
Elbow flexion	27.0 \pm 9.4
Shoulder abduction	26.5 \pm 9.9
Ankle dorsiflexion	27.2 \pm 10.2
Knee extension	29.5 \pm 5.9
Hip flexion	29.0 \pm 6.9
Upper limb total	80.4 \pm 28.8
Lower limb total	86.6 \pm 21.6
Side total	83.6 \pm 24.5

Table 36. The Motricity Index scores (mean \pm S.D.) for the 74 patients examined at 12 months.

The relationship of the Motricity Index with central motor conduction

All patients were able to contract voluntarily target muscles of the non-paretic limb irrespective of the degree of paresis of the paretic limb. If a response was present in the target muscles of the paretic limb following cortical stimulation, whether the CMCT was normal or delayed, voluntary movement of the muscle was usually present. However, the presence of a response in a target muscle did not correlate with normal power and the muscle was often profoundly weak. In contrast, 12 patients with no movement of pinch grip at Day 1 did have recordable responses in the thenar muscles, 10 with normal CMCTs and two with delayed CMCTs. Similar absence of movement but with preservation of responses was seen in all the target muscles on Days 1-7.

Patients with no responses recorded in a target muscle following EMS of the cortex, invariably demonstrated either absolutely no movement or occasionally a flicker of movement in the muscle. Two individuals appeared to be exceptions to this observation, both had slightly more than a flicker of movement in the target muscles despite the absence of recordable responses following cortical stimulation.

The patients were divided into three groups using the results of CMCT recorded from the thenar muscles. Patients were divided into Normal, Delayed and No Response Groups. The median scores on the paretic side for the pinch grip, the arm as a whole, the leg as a whole and for the paretic side (arm and leg together) are shown in Fig. 9. Significant differences were found when the three groups were compared for all measures of strength. The No Response Group of patients always demonstrated the lowest scores.

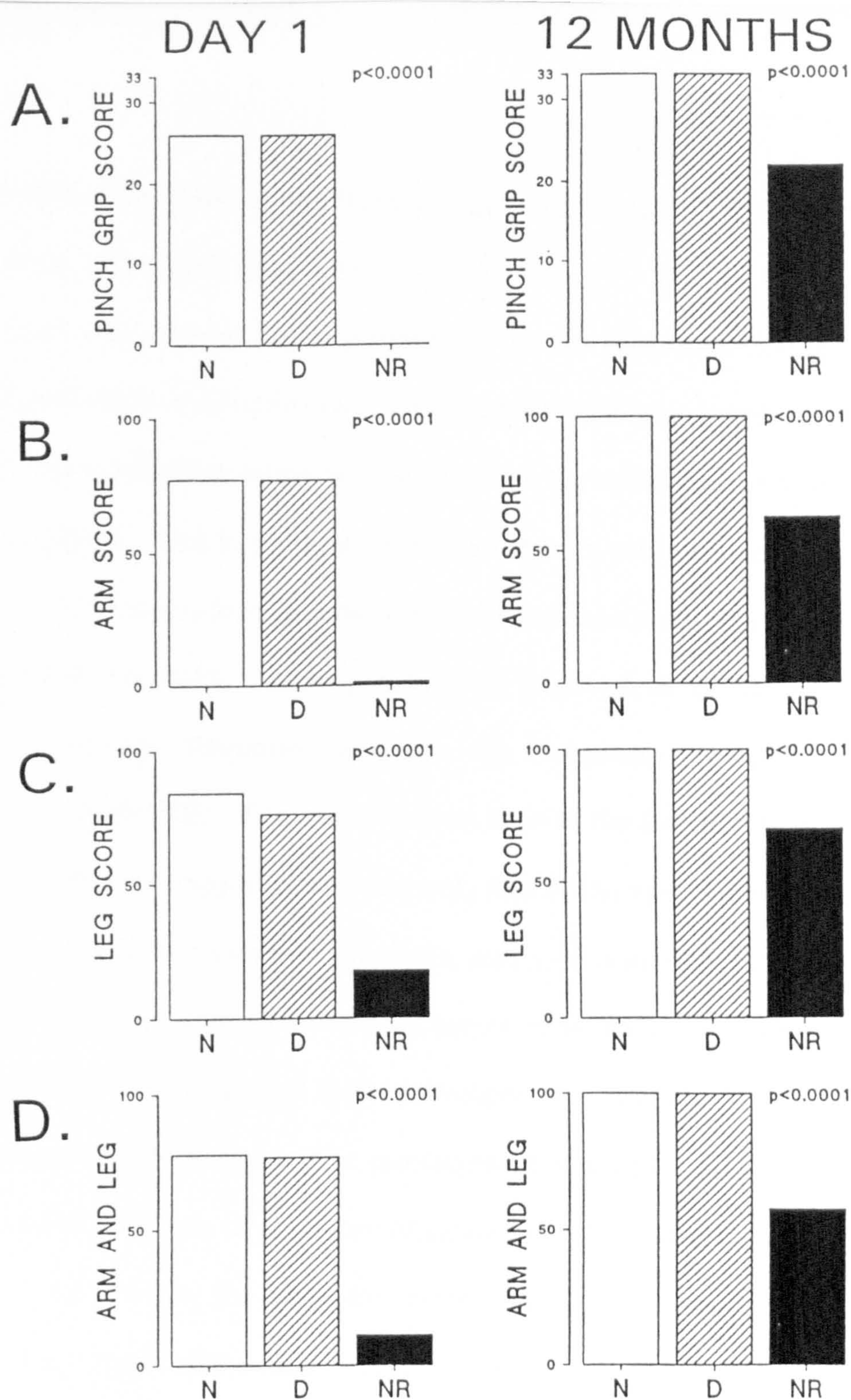


Figure 9. Comparison of Motricity scores for the three groups of patients at Day 1 and 12 months. Kruskal Wallis analysis of variance identifies differences between the three groups at each time of testing.

- N** Normal Response Group
- D** Delayed Response Group
- NR** No Response Group

When the three conduction groups were compared there was a significant difference for median pinch grip strength at Day 1. The No Response Group had a median value of zero. Four patients in the No Response Group had a flicker of muscle activity and a further two subjects had some very weak movement. Similar results were obtained when the strength of the other muscles in the upper limb was compared. The lower limb muscles retained more power (Fig. 9C).

At 12 months most the patients had regained some muscle strength in both upper and lower limbs. The improvements in power at 12 months for patients in both the Normal Response and the No Response Groups were significant (Wilcoxon, $p < 0.005$). The improvement seen in the Delayed Response Group did not reach statistical significance, but only five of the seven patients in the Delayed Response Group survived to 12 months, and so the result may be skewed. When muscle strength for all the movements tested in the Motricity Index were compared for the Normal Response and Delayed Response Groups at 12 months there were no significant differences. The presence of delayed CMCT at Day 1 did not influence the outcome of recovery of power at 12 months.

At 12 months the outcome strengths were compared for the surviving patients from each of the Day 1 conduction groups. In each case patients were allocated to their original groups, irrespective of any changes that may have occurred in CMCT by 12 months. Despite an improvement in the median scores for each group, the No Response Group had significantly lower scores compared to the Normal and Delayed Response Groups. The same differences in muscle strength between the three groups were present using the results from any of the target muscles to formulate the three conduction groups. The most significant

differences were seen when the results of CMCTs for the thenar muscles were divided into the three conduction groups and the groups were compared.

Therefore, when the three conduction groups are compared the differences in muscle strength at Day 1 are significant. Differences between the groups were still present at 12 months. Both at Day 1 and at 12 months the No Response Group achieved the lowest scores. The results for Day 1 CMCTs of any of the four target muscle can be used to divide the patients into the three conduction groups. Similar correlations were seen for each of the target muscles. The No Response Group had the lowest scores at Day 1 and the survivors of this group made the least recovery of muscle power. Significant differences were present when the median values of scores for the whole arm, or for the power of the whole of the paretic side of the body were compared for the three conduction groups at Day 1 and for the survivors at 12 months. The power of triceps brachii and pectoralis major were not assessed as part of the Motricity Index. However, if the results from these muscles were used to subdivide the patients into the three conduction groups, if responses were absent at Day 1 the outcome was poor at 12 months.

3.7.6 The Nine-hole Peg Test of hand dexterity after stroke

The Nine-hole Peg Test at Day 1

The mean rate for the Peg Test for normal healthy subjects was 0.55 ± 0.07 S.D. pegs per second. The scores for the Peg Test at Day 1 using the patients paretic and non-paretic hands are given in Table 37A. 90 patients were able and 28 patients were unable to attempt the test at Day 1. 21 patients with no useful

PEG TEST RATE FOR PATIENTS AT DAY 1	
Paretic hand (n=111)	0.07 \pm 0.12 pegs/sec
Non-paretic hand (n=90)	0.33 \pm 0.1 pegs/sec

Table 37A. The peg test rate (mean \pm S.D.) for the 111 patients assessed at Day 1. The results for the paretic hand includes the 21 patients who were assigned scores of zero.

PEG TEST RATE FOR PATIENTS AT 12 MONTHS (n=73)	
Paretic hand	0.28 \pm 0.21 pegs/sec
Non-paretic hand	0.45 \pm 0.13 pegs/sec

Table 37B. The peg test rate (mean \pm S.D.) for the 73 surviving patients assessed at 12 months.

pinch grip in the affected hand (Motricity scores of zero or nine) were unable to make any attempt to perform the peg test at Day 1. In the absence of no useful hand movements it was assumed that a number of non-motor deficits e.g. visual or cognitive were adversely inhibiting the patients from attempting the test. The 21 patients were assigned scores of zero i.e. no pegs positioned (See: 2.2.4 Clinical assessments - The Nine-hole Peg Test of hand dexterity). The patients were unable to perform the Peg Test with their non-paretic hand. However, because muscle strength was not lost in the non-paretic hand, they were not assigned scores of zero. It was therefore not correct to make the same assumption that the non-paretic hand was incapable of achieving a score if the particular neurological deficit that prevented the test had been removed.

A further seven patients who could not attempt the test, were not assigned scores of "no pegs positioned". These patients had neurological problems that limited hand dexterity but they had preservation of power of pinch grip greater than no movement or a flicker of movement and so potentially may have been able to grasp the pegs if the other inhibitory defects had not been present.

The Nine-hole Peg Test at 12 months after stroke

Three patients were unable to perform the test at 12 months, one was moribund and two patients had moved from the Region. Most patients demonstrated some improvement of hand dexterity at 12 months. No patients had arbitrary scores of zero assigned to them since all the patients could attempt the test. The results at 12 months are shown in Table 37B.

The relationship of the Nine-hole Peg Test to central motor conduction

In the No Response Group at Day 1 only six patients had voluntary movement of the muscles used in the pinch grip test of the Motricity Index. Only one of the six patients was able to place a single peg in the 50s allowed. The scores for the remaining patients of the No Response Group were zero (Fig. 10). The one patient able to perform the test was one of two patients who had more than just a flicker of movement in the Motricity Index assessment of pinch grip but no responses in the thenar muscles following cortical stimulation at Day 1. At 12 months 16 out of the 19 surviving patients of the No Response Group were available to attempt the test. Only two achieved scores in the normal range. These were the same two patients, who demonstrated muscle movement but had no recordable responses (See: 3.7.5 The Motricity Index of muscle power after stroke - The relationship of the Motricity Index with central motor conduction).

When the median rates of peg positioning at Day 1 for the three conduction groups defined by the thenar muscles were compared the results were significant. Despite improvements in muscle power and hand dexterity for each group, the surviving patients from the No Response Group continued to demonstrate significantly lower levels of performance at 12 months. Patients with no responses following cortical stimulation at Day 1 (the No Response Group) appear to have a poor prognosis for manual dexterity.

For those patients in the Normal or Delayed Response Groups the initial performance is similar but they recover to different levels of performance. At Day 1 a few pegs can be placed but the peg rate is well outside the normal range.

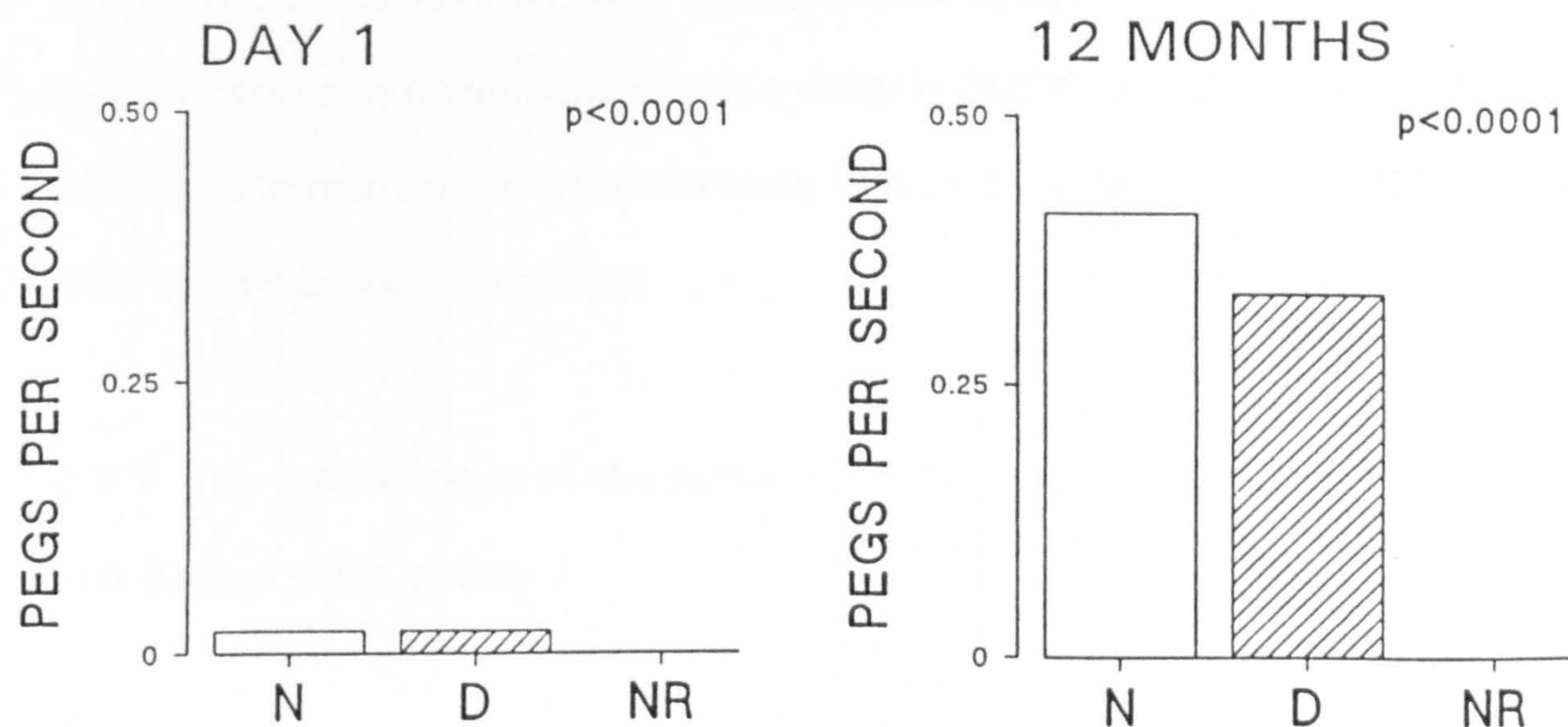


Figure 10. Comparison of the Nine-hole Peg Test rate for the three groups of patients at Day 1 and at 12 months. Kruskal Wallis analysis of variance identifies differences between the three groups at each time of testing.

- N** Normal Response Group
- D** Delayed Response Group
- NR** No Response Group

By 12 months significant improvement has taken place with the median value of the Normal Response Group within the normal range and that of the Delayed Response Group remaining just outside. Using a Mann-Whitney test to compare the differences in performance at 12 months between the Normal and Delayed Response Groups the results were not significantly different. However, the median score for the five surviving patients of the original seven patients of the Delayed Response Group was below the normal range. The results are based upon a very small group of patients and may not be accurate, but they suggest that abnormal central motor conduction resulting in a delay in CMCT identifies a group of patients in whom the recovery of hand dexterity is likely to be less complete than patients with normal conduction values.

3.7.7 The Barthel scale of the activities of daily living after stroke

The Barthel scale at Day 7

At Day 7, 106 patients were alive and 12 had died. The surviving patients were assessed using the Barthel scale. The patient's carer was questioned regarding all aspects of the activities of daily living. The individual's ability to perform many activities was unknown. This was due to the fact that the patient had remained ill in bed and had not been given the opportunity to try certain activities. The activities most frequently not known were the ability to climb stairs and bathing. Incomplete scores were surprisingly frequent despite the fact the patient had been in hospital for seven or more days by the time the first assessment was made.

A wide range of scores were present at Day 7, with some patients scoring full marks in some categories, others had scores of zero. The median Barthel score for patients at Day 7 was 9.0 ± 6.7 S.D. (Table 38).

The Barthel scale at 12 months after stroke

Details on all 76 surviving patients were available at 12 months and provided a final Barthel score. The median score for the survivors at 12 months was 19.5 ± 4.4 S.D. (Table 39). Most patients demonstrated some improvement in the ability to perform the activities of daily living. Bathing, the use of stairs, grooming and dressing were the activities least likely to improve.

The relationship of the Barthel scale at 12 months after stroke to central motor conduction

The surviving patients were subdivided arbitrarily into poor and good outcome groups at 12 months. There were 64 patients with good outcome (scores of 13-20) and 12 with poor outcome (scores of 0-12) (Table 40). 58% of the patients with poor outcome originally had no responses at Day 1 whereas 42% of patients with poor outcome were patients who did have responses at Day 1 (Delayed and Normal Groups combined). Proportionally more surviving patients with no responses at Day 1 (35%) had a poor outcome at 12 months compared to the proportion of survivors from patients with responses at Day 1 (9%). The number of patients with no responses at Day 1 in the poor outcome group at 12

BARTHEL SCALE OF THE ACTIVITIES OF DAILY LIVING AT DAY 7.			
	Score	Patients (n = 106)	
Bowel control	0 =	14	(11.9%)
	1 =	3	(2.5%)
	2 =	74	(62.7%)
Bladder control	0 =	27	(22.9%)
	1 =	2	(1.7%)
	2 =	64	(54.2%)
Grooming	0 =	46	(39.0%)
	1 =	47	(39.8%)
Toilet use	0 =	36	(30.5%)
	1 =	26	(22.0%)
	2 =	31	(26.3%)
Feeding	0 =	8	(6.8%)
	1 =	56	(47.5%)
	2 =	29	(24.6%)
Transfer	0 =	9	(7.6%)
	1 =	49	(41.5%)
	2 =	3	(2.5%)
	3 =	32	(27.1%)
Mobility	0 =	47	(39.8%)
	1 =	1	(0.8%)
	2 =	16	(13.6%)
	3 =	29	(24.6%)
Dressing	0 =	41	(34.7%)
	1 =	31	(26.3%)
	2 =	21	(17.8%)
Stairs	0 =	2	(1.7%)
	1 =	3	(2.5%)
	2 =	23	(19.5%)
Bathing	0 =	38	(32.2%)
	1 =	25	(21.2%)
Median total = 9.0 ± 6.7 S.D.			

Table 38. The Barthel scores for the surviving 106 patients assessed at Day 7.

BARTHEL SCALE OF THE ACTIVITIES OF DAILY LIVING AT 12 MONTHS.			
	Score	Patients (n = 76)	
Bowel control	0 =	1	(1.3%)
	1 =	0	(0%)
	2 =	75	(98.7%)
Bladder control	0 =	2	(2.6%)
	1 =	4	(5.3%)
	2 =	70	(92.1%)
Grooming	0 =	15	(19.7%)
	1 =	61	(80.3%)
Toilet use	0 =	7	(9.2%)
	1 =	9	(11.8%)
	2 =	60	(79.0%)
Feeding	0 =	3	(4.0%)
	1 =	27	(35.5%)
	2 =	46	(60.5%)
Transfer	0 =	0	(0%)
	1 =	10	(13.1%)
	2 =	5	(6.6%)
	3 =	61	(80.3%)
Mobility	0 =	2	(2.6%)
	1 =	4	(5.3%)
	2 =	8	(10.5%)
	3 =	62	(81.6%)
Dressing	0 =	10	(13.1%)
	1 =	22	(29.0%)
	2 =	44	(57.9%)
Stairs	0 =	17	(22.4%)
	1 =	7	(9.2%)
	2 =	52	(68.4%)
Bathing	0 =	32	(42.1%)
	1 =	44	(57.9%)
Median total = 19.5 ± 4.4 S.D.			

Table 39. The Barthel scores for the surviving 76 patients assessed at 12 Months.

BARTHEL OUTCOME	NORMAL RESPONSE GROUP	DELAYED RESPONSE GROUP	NO RESPONSE GROUP
Poor outcome	4	1	7
Good outcome	47	4	13

Table 40. The Barthel scores for surviving patients at 12 months divided into good (scores 13-20) and poor (0-12) outcome groups.

months might have been even greater if more than 50% of them had not died (See: 3.7.9 Mortality after stroke). The surviving patients who originally had responses at Day 1 (the Delayed and Normal Groups combined) had a low probability of poor outcome and the probability of good outcome was high.

Fig. 11 shows that the No Response Group had very low Barthel scores at Day 7 and, although the subjects had improved by 12 months, they did not achieve maximal scores. Once again the scores of the Normal and Delayed Response Groups are similar and start at Day 7 significantly better than those of the No Response Group. Both improve to reach maximal median scores at 12 months. The differences at Day 7 between the three groups of subjects are still present and remain significant at 12 months.

Unlike the other functional assessments the Barthel score utilised the information obtained at Day 7. A period of time was required to assess whether the subject could perform many of the activities. If the Barthel score was assessed earlier after stroke it was not reliable. It should be noted, however, that the patients were still grouped according to central motor conduction at Day 1. Since 12 patients had died before their Day 7 test the influence of this subgroup with exceptionally poor prognosis is unknown. A further reason for error when comparing Day 7 scores was the surprisingly incomplete assessment given by the carers of the patient's ability to perform the activities of daily living.

The Barthel score, subdivided arbitrarily into good and poor outcome groups (Table 40) is expressed as an odd's ratio in Fig. 12. The surviving patients from the No Response Group at Day 1 compared to the patients with responses, whether normal or delayed at Day 1, have a higher probability of poor outcome.

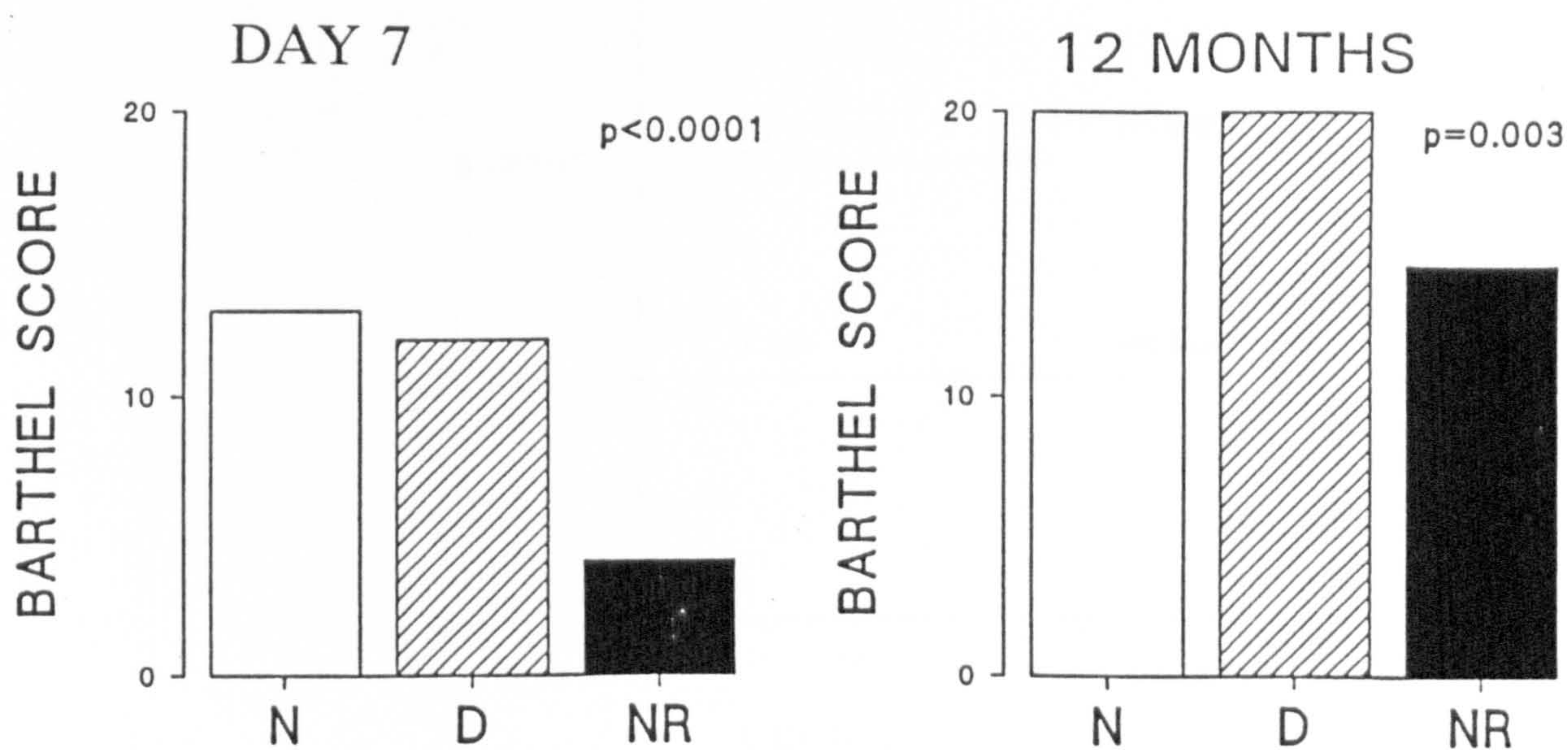


Figure 11. Comparison of Barthel scores for the three groups of patients (using the Day 1 conduction results) at Day 7 and at 12 months. Kruskal Wallis analysis of variance identifies differences between the three groups at each time of testing.

- N** Normal Response Group
- D** Delayed Response Group
- NR** No Response Group

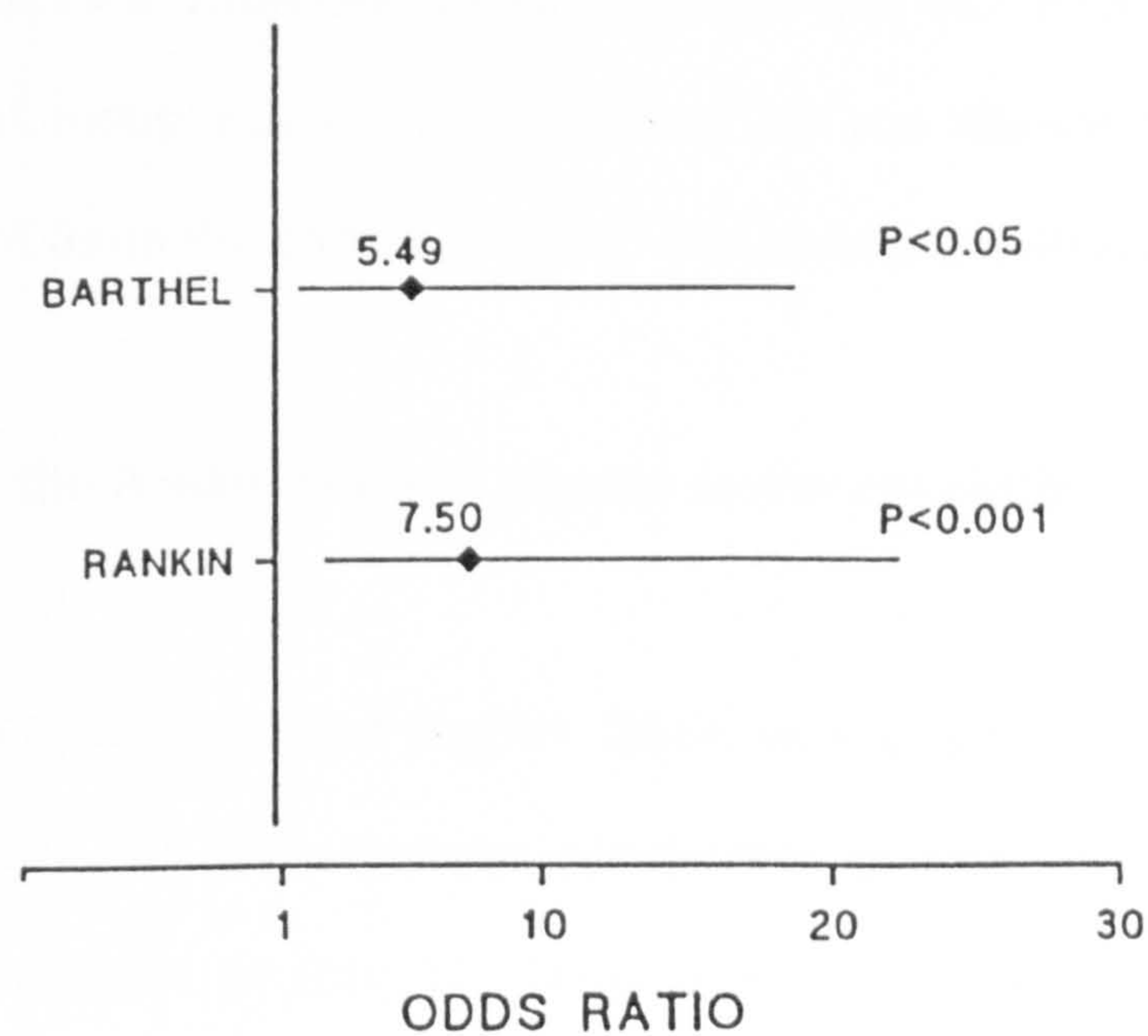


Figure 12. Graphical representation of odds ratio with respect to poor outcome at 12 months assessed by the Barthel score and Rankin scale. Patients in the No Response Group at Day 1 are compared with those of the combined Normal and Delayed Responses groups at Day 1. The diamond with the value above gives the odds ratio and the horizontal line the 95% confidence interval. The significance is given by the Chi-squared test.

3.7.8 The Rankin scale of functional outcome at 12 months after stroke

At 12 months the 76 surviving patients were allocated a level of functional outcome using the modified version of the Rankin scale. At 12 months only three patients (2.5%) were completely free of symptoms and had no impairment of function resulting from their stroke. The patients were also divided into two groups, those who were independent (categories 0, 1 and 2) and those who were dependent upon the care of others (categories 3, 4 and 5). 59% of patients had achieved a level of independence as measured by the Rankin scale and 41% remained dependent upon the care of others. The results are shown in Table 41A.

The relationship of the Rankin scale to central motor conduction

At 12 months the modified Rankin Scale was used to assess functional outcome in relation to the three patient conduction groups with respect to the thenar muscles as defined at Day 1. Table 41B demonstrates the number of patients in each grade of the Rankin scale for each of the original conduction groups. Fig. 13 shows the results graphically for all the survivors from each conduction group for each Rankin grade.

The No Response Group had the worst outcome with 76% (16/21) of the survivors remaining dependent. A smaller proportion of patients with no responses at Day 1 (11% i.e. 5/44) achieved independence compared to the 54% (40/74) who survived from the combined Normal and Delayed Response Groups at Day 1 who achieved independence.

RANKIN OUTCOME GROUP	RANKIN SCALE	NUMBER OF PATIENTS
Independent (n = 45)	Grade = 0	3
	Grade = 1	23
	Grade = 2	19
Dependent (n = 31)	Grade = 3	14
	Grade = 4	15
	Grade = 5	2

Table 41A. The number of patients in each grade of the Rankin scale at 12 months. The number in each Rankin outcome group is also given.

RANKIN	NORMAL	DELAYED	NO RESPONSE
0	3	-	-
1	20	2	1
2	13	2	4
3	9	-	5
4	5	1	9
5	1	-	1

Table 41B. The surviving patients (n = 76) from the original conduction groups (thenar muscles) from Day 1 in each Rankin catagory at 12 months.

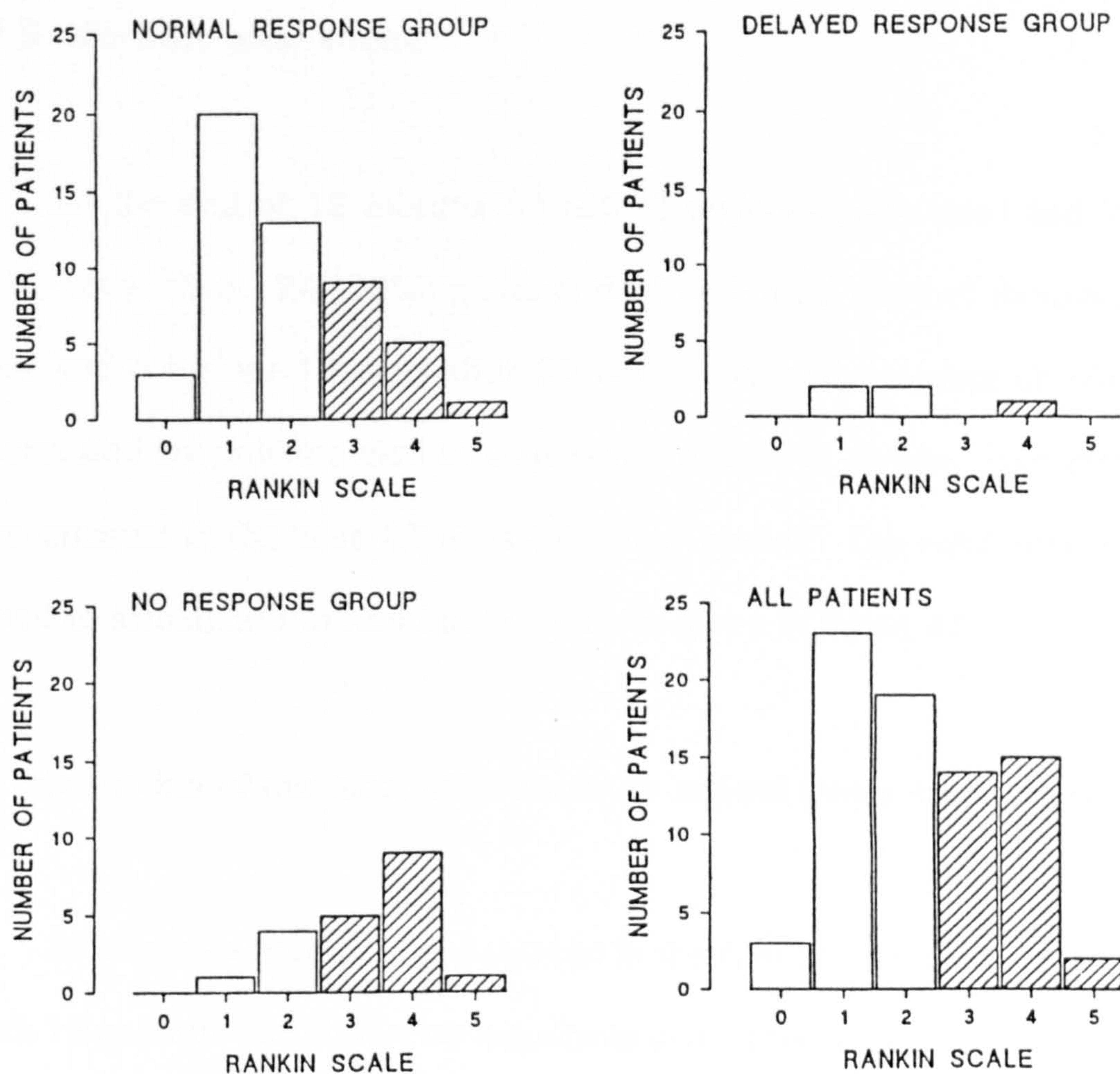


Figure 13. Distribution of Rankin scale scores among the Normal Response Group, Delayed Response Group, No Response Group and all three Groups combined. The open bars indicate independence and the hatched bars dependence as assessed by the Rankin scale.

The value of subdividing the Rankin Scale into dependent and independent groups is expressed as an odd's ratio in Fig. 12. The No Response Group compared to those with responses, whether normal or delayed, have a higher probability of poor outcome and remaining dependent.

3.7.9 Mortality after stroke

At the end of 12 months 42 (36%) patients were dead and 76 patients (64%) were alive. 24 (20%) patients died within 28 days of recruitment to the study and a further 18 died after 28 days. 36 patients died of stroke-related causes, and six patients died of causes not related to stroke. Non-stroke deaths were unusual in the first 28 days following stroke. The relationship of causes related to stroke and to non-stroke death is given in Table 42.

The relationship of mortality after stroke to central motor conduction

23 stroke-related deaths occurred in the first 28 day period after stroke, of which 15 patients had shown no responses in the thenar muscles following cortical stimulation at Day 1. There were a total of 36 stroke-related deaths at 12 months, of which 23 patients had shown no responses in the thenar muscles following cortical stimulation at Day 1 (Table 43).

When patients with no responses in the thenar muscles on one or more occasions on Days 1-7 were reviewed, they were found to account for 18 of the 23 deaths in the first 28 days, and 28 of the 36 stroke-related deaths by 12

TIME OF DEATH	STROKE-RELATED DEATH	NON-STROKE DEATH
Within 28 days	23	1
Between 28 days and 12 months	13	5

Table 42. Timing of death whether within 28 days or between 28 days and 12 months after stroke and the relationship to the cause of death.

MORTALITY AT 28 DAYS

MUSCLE WITH NO RESPONSE	STROKE-RELATED DEATH (n=23)	DEATH UNRELATED TO STROKE (n=1)	ALIVE (n=94)
Thenar. Day 1 (n=44)	15	1	28
Thenar. Days 1-7 (n=53)	18	1	34
Any muscle. Days 1-7 (n=63)	20	1	42

MORTALITY AT 12 MONTHS

MUSCLE WITH NO RESPONSE	STROKE-RELATED DEATH (n=36)	DEATH UNRELATED TO STROKE (n=6)	ALIVE (n=76)
Thenar. Day 1 (n=44)	23	1	20
Thenar Days 1-7 (n=53)	28	1	24
Any muscle. Days 1-7 (n=63)	31	4	28

Table 43. The number of patients who died at 28 days and at 12 months are given with the numbers dying of stroke-related and unrelated causes for patients with absent responses divided into the following groups:

1. No Response in the thenar muscles at Day 1.
2. No responses in the thenar muscles on one or more occasions on Days 1-7.
3. No responses in any one or more than one target muscle, on one or more occasions on Days 1-7.

months. More significantly, when the patients who demonstrated no responses in any one or more than one target muscle, on one or more occasions on Days 1-7 were considered, they accounted for 20 of the 23 stroke-related deaths occurring in the first 28 days and 31 of the 36 stroke-related deaths at 12 months. Therefore, of the 36 stroke-related deaths at 12 months only five deaths were in patients who demonstrated responses in all of the target muscles on Days 1-7. Of these five patients, responses in relaxed muscles were recorded in only three patients. In both cases where responses could not be obtained in relaxed muscles, a response was possible with muscle contraction. Therefore only three patients (8%) out of 36 who died of stroke-related causes had entirely normal central motor conduction. 33 (92%) out of the 36 deaths occurred in patients with conduction abnormalities. It is also worth noting that four out of the six patients who died of causes defined as unrelated to stroke did not have responses in any one or more than one target muscle, on one or more occasions on Days 1-7.

A total of 24/53 patients (45%) with absent responses in the thenar muscles at Days 1-7 survived to 12 months and a similar proportion of the 28/63 patients (44%) with no responses in any one or more than one target muscle, on one or more occasions on Days 1-7. In contrast 48/55 patients (87%) with responses always present in all target muscles on Days 1-7 survived to 12 months and only five (9%) of this group died of stroke-related causes by 12 months. The chances of dying increase when responses are absent in one, or more than one target muscle on Days 1-7 after stroke compared to abnormalities identified at Day 1 (Fig. 14). The Day 1 test is highly predictive of outcome but if the stroke extends the risk of death increases and this is identified by using the results on Days 1-7.

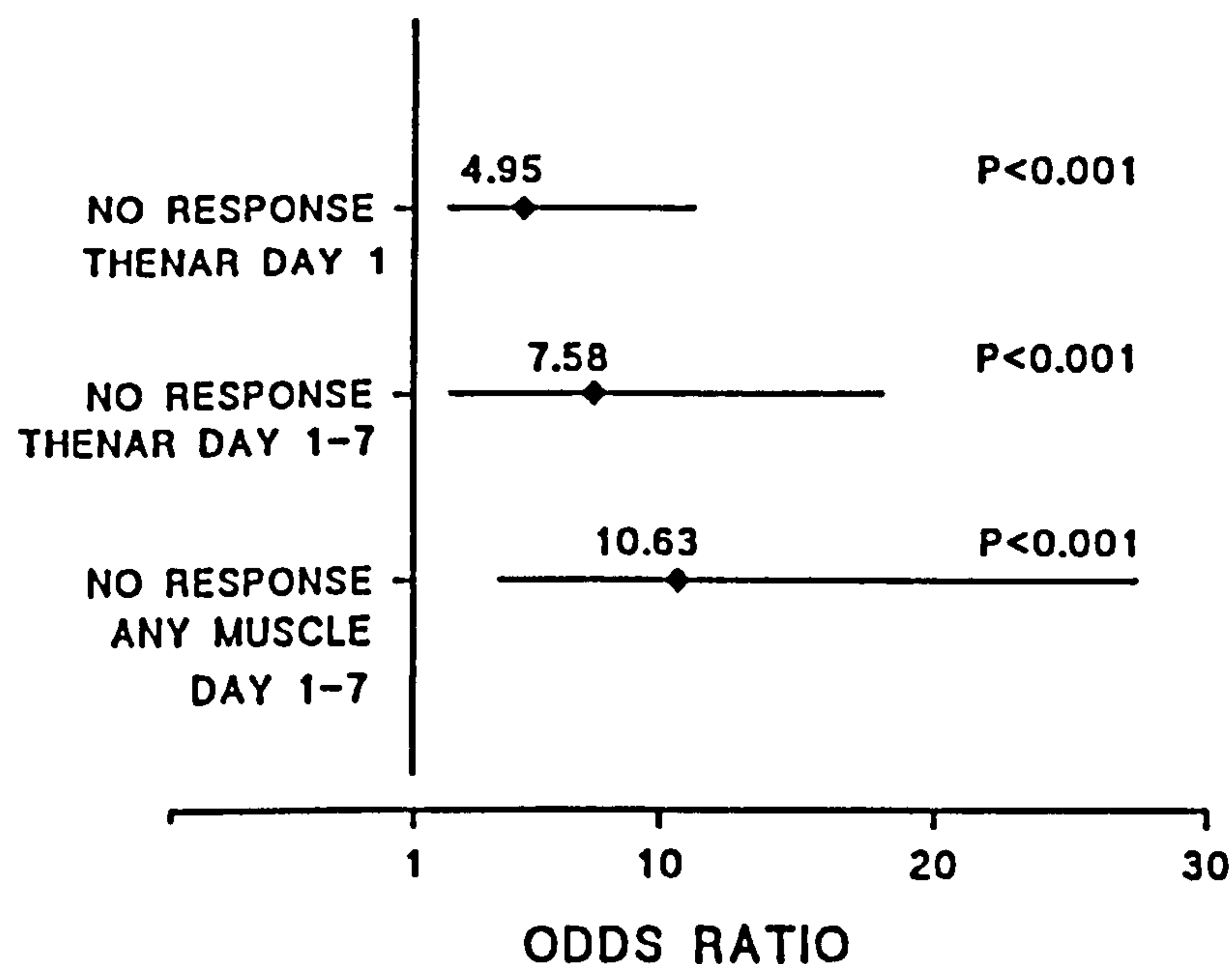


Figure 14. Graphical representation of odds ratio with respect to stroke-related death, illustrating three different No Response Groups:

1. No response in the thenar muscles at Day 1.
2. No responses in the thenar muscles on one or more occasions on Days 1-7.
3. No responses in any one or more than one target muscle, on one or more occasions on Days 1-7.

The diamond with the value above gives the odds ratio and the horizontal line the 95% confidence interval. The significance is given by the Chi-squared test.

The absence of responses in the thenar muscles (or any single muscle) within 72 hours of stroke, in the thenar muscles (or any single muscle) on one or more occasions on Days 1-7, or the absence of responses in one or more muscle on one or more occasions on Days 1-7 correlated with an increased probability of death. Absent responses following cortical stimulation increases the risk of death. If the damage evolves in the first few days after stroke, resulting in further loss of responses in more than one muscle, the probability of death increases.

3.7.10 The period of time after stroke to death

Surprisingly all the patients who died of stroke-related causes died in hospital. The mean time to death was 57.9 days. The six patients who died of causes unrelated to stroke did so much later, mean = 157.7 days. The period of time after stroke to death was not significantly different when patients with no responses following cortical stimulation were compared to those who died who did have responses, whether the comparisons are made at Day 1 ($p=0.20$), or on Days 1-7 ($p=0.40$).

3.7.11 The duration of stay in hospital after stroke

The mean stay in hospital to death or discharge for all 118 patients was 62.5 days. Patients who survived to 12 months had a mean stay of 67.2 days (Table 44). Patients with responses present on Day 1 or on Days 1-7 had shorter stays in hospital than patients with no responses on these days.

PATIENTS		DAYS IN HOSPITAL
Total number of patients	(n = 118)	62.5 \pm 79.2
Survivors at 12 months	(n = 76)	67.2 \pm 85.7
No response in thenar muscles at Day 1	(n = 44)	81.4 \pm 84.1
Responses in thenar muscles at Day 1	(n = 74)	51.3 \pm 74.4
Patients who die:		
total	(n = 42)	72.5 \pm 80.3
stroke-related death	(n = 36)	57.9 \pm 72.7
non-stroke death	(n = 6)	157.7 \pm 73.7
No response in thenar muscles Days 1-7 (n = 53) ¹ :		
stroke-related deaths	(n = 28)	55.9 \pm 70.7
survivors	(n = 24)	109.6 \pm 83.4
Responses present in thenar muscles Days 1-7 (n = 65) ² :		
stroke-related deaths	(n = 8)	20.1 \pm 17.2
survivors	(n = 52)	47.7 \pm 80.2

Table 44. The duration of stay in hospital (mean \pm S.D.) for different groups of stroke patients.

¹ One patient died of causes unrelated to stroke.

² Five patients died of causes unrelated to stroke.

The relationship of duration of stay in hospital after stroke to central motor conduction

When the means for the number of days a patient remained in hospital were compared for different patient groups, the 24 surviving patients, who had no responses in the thenar muscles at any time on Days 1-7, remained in hospital for 109 days, which was significantly longer than the 47 day period for the 52 surviving patients from the Normal and Delayed Response Groups combined, who always had responses in the thenar muscles on Days 1-7 (Table 45). Surviving patients from the No Response Group at Day 1 had a considerably longer stay in hospital than patients with responses from the Normal and Delayed Response Groups combined at Day 1. Although this measure is influenced by many non-medical factors it reflects the incomplete recovery and loss of independence seen in the patients who had no responses following cortical stimulation.

3.8 THE INFLUENCE OF STROKE PROGRESSION ON OUTCOME AT 12 MONTHS

Although many physical signs develop rapidly after stroke, damage may progress over a number of days leading to further loss of function. With this in mind, it has been useful to refer to patients with no responses following cortical stimulation on one or more occasions in the period Day 1 to Day 7. This increased the number of patients in the No Response Group in the thenar muscles to 53 patients by including those whose stroke had progressed and who subsequently lost responses following cortical stimulation. When patients in the Days 1-7 No

PATIENT GROUP	DURATION IN HOSPITAL	SIGNIFICANCE
No response Days 1-7	109.6 \pm 83.4	p=0.0001
Responses present Days 1-7	47.7 \pm 80.2	

Table 45. The length of stay in hospital of patients with no response in the thenar muscles following cortical stimulation on Days 1-7 compared to patients with responses on Days 1-7 (Mann-Whitney).

Response Group are compared to patients with no responses following cortical stimulation at Day 1, the mean values for most outcome measures are less and there was an increase in the number of patients in the poor outcome groups. The correlations for some of the major outcome assessments are more significant for patients in the Days 1-7 No Response Group. These values are given in Table 46. In each case patients with responses were compared to those without responses.

3.9 THE INFLUENCE OF THE NUMBER OF MUSCLES WITH NO RESPONSES FOLLOWING CORTICAL STIMULATION ON OUTCOME AT 12 MONTHS

Poor outcome was related to the number of target muscles demonstrating absent responses - the more muscles with absent responses the less favourable the outcome. Table 47 shows the number of patients relative to the number of muscles with no responses following cortical stimulation.

When the major outcome measures are compared for all the patients with absent responses in one or more target muscles on one or more occasions on Days 1-7, some of the correlations were stronger (Table 48 - compare to Table 46). The number of muscles with absent responses is probably an indication of the extent of damage to the motor pathways. The more muscles with no responses following cortical stimulation at anytime on Days 1-7 post-stroke, the stronger the correlation to final poor outcome and the more accurate the prognostic value of evaluating central motor conduction.

12 MONTHS OUTCOME	NO RESPONSE DAY 1(n=44)	p VALUE	NO RESPONSE DAYS 1-7 (n=53)	p VALUE
Motricity Index: (mean \pm S.D.)				
Pinch grip	15.1 \pm 12.1	p<0.0001	14.9 \pm 11.3	p<0.0001
Arm total	52.5 \pm 37.2	p=0.0001	51.7 \pm 35.0	p<0.0001
Leg total	67.4 \pm 28.7	p=0.0001	68.0 \pm 27.1	p<0.0001
Arm+leg total	59.9 \pm 32.0	p=0.0001	59.8 \pm 29.9	p<0.0001
Peg test rate (mean \pm S.D.)	0.06 \pm 0.14	p<0.0001	0.05 \pm 0.13	p<0.0001
Barthel:				
median score	14.5 \pm 5.1	p<0.005	13.5 \pm 4.8	p<0.0001
poor outcome	7	p<0.05	8	p<0.0001
Rankin:				
poor outcome	15	p<0.001	19	p<0.0001
Stroke-related deaths	23	p<0.001	28	p<0.001

Table 46. The mean values \pm S.D. and the number of patients in each poor outcome group for patients with no response in the thenar muscles on Day 1 and also for patients with no responses on Days 1-7. The p values refer to the significance of the differences for the scores of those with no responses at Day 1 compared to those with responses at Day 1, and the differences between those with no responses on one or more occasions on Days 1-7 compared to those who always had responses Days 1-7.

NUMBER OF MUSCLES WITH NO RESPONSES ON ONE OR MORE OCCASIONS DAYS 1-7	NUMBER OF PATIENTS
None	55 (46.6%)
1 muscle	4 (3.4%)
2 muscles	5 (4.2%)
3 muscles	11 (9.3%)
4 muscles	43 (36.4%)

Table 47. Number of patients demonstrating muscles with no responses on one or more occasions on Days 1-7.

12 MONTHS OUTCOME	NO RESPONSE IN ONE OR MORE TARGET MUSCLES ON ONE OR MORE OCCASIONS ON DAYS 1-7 (n=63)	RESPONSES IN ALL TARGET MUSCLES ON ALL OCCASIONS DAYS 1-7 (n=55)	p VALUE
Motricity Index: (mean \pm S.D.)			
Pinch grip	16.4 \pm 11.2	30.7 \pm 4.6	p<0.0001
Arm total	54.0 \pm 33.0	94.7 \pm 10.8	p<0.0001
Leg total	67.4 \pm 25.5	97.0 \pm 8.2	p<0.0001
Arm+leg total	60.7 \pm 27.8	95.9 \pm 8.6	p<0.0001
Peg test rate (mean \pm S.D.)	0.06 \pm 0.12	0.39 \pm 0.15	p<0.0001
Barthel:			
median score	13.8 \pm 4.6	20.0 \pm 3.2	p<0.0001
poor outcome	10.0	2.0	p<0.0005
Rankin:			
poor outcome	23.0	8.0	p<0.0001
Stroke-related deaths	31.0	5.0	p<0.0001

Table 48. Mean outcome values (\pm S.D.) for patients with one or more muscles with no responses on one or more occasions on Days 1-7 compared to patients who always had responses in all muscles on Days 1-7. The p value refers to the significance when the two groups are compared for each outcome value.

3.10 THE RELATIONSHIP OF THRESHOLD TO ELECTROMAGNETIC STIMULATION ON OUTCOME AT 12 MONTHS

Responses at Day 1 could be grouped as:

- 1) Obtained in relaxed muscles.
- 2) Only obtained with muscle contraction with maximum EMS.
- 3) Absent despite maximum stimulation and muscle contraction.

In many stroke patients responses could not be evoked in relaxed muscles and contraction was required to facilitate a response. The threshold for responses in stroke patients was graded not only by the level of output of the stimulator, but the need for contraction when responses were not present at maximum stimulator power output in relaxed muscle. This phenomenon was observed for all target muscles but was only documented for biceps brachii (Table 49).

The outcome of patients in whom responses in biceps brachii were only possible with muscle contraction was compared with those with responses in relaxed biceps brachii. Patients who required muscle contraction at Day 1 to produce a response, had mean clinical and functional outcome scores slightly lower than patients with responses in relaxed muscle. If contraction was required to facilitate a response a larger proportion of patients either died or achieved poor outcome in terms of Barthel and Rankin outcome groups. However when the differences were analysed they failed to reach statistical significance.

Analysis of the relationship to death revealed some interesting observations. Of the 23 stroke-related deaths that occurred within 28 days after stroke, 14 were patients with no responses recorded in the biceps brachii on Day 1. A further five

12 MONTHS OUTCOME	RESPONSES IN RELAXED BICEPS BRACHII MUSCLE DAY 1 (n=53)	RESPONSES ONLY IN CONTRACTED BICEPS BRACHII MUSCLE DAY 1 (n=19)
Motricity Index: (mean \pm S.D.)		
Pinch grip	30.3 \pm 5.5	26.4 \pm 7.1
Arm total	93.6 \pm 14.7	80.1 \pm 19.1
Leg total	96.0 \pm 9.2	85.4 \pm 20.2
Arm+leg total	94.9 \pm 11.1	82.9 \pm 18.4
Peg test rate (mean \pm S.D.)	0.36 \pm 0.17	0.26 \pm 0.24
Barthel:		
median score	20.0 \pm 2.5	20.0 \pm 5.1
poor outcome	3.0 (5.6%)	2.0 (8.7%)
Rankin:		
poor outcome	11.0 (20.4%)	5.0 (21.7%)
Stroke-related death	7.0 (13.0%)	7.0 (30.4%)

Table 49. The mean values and number of patients in outcome groups and number of stroke-related deaths for patients with responses obtained in relaxed biceps brachii muscles and those in whom responses could only be obtained in conjunction with contraction of the target muscle or the homologous muscle.

deaths occurred in those in whom responses could only be obtained at 100% electromagnetic output with the additional threshold-lowering effect of muscle contraction. Therefore, of the 23 stroke-related deaths occurring within 28 days of stroke, all except four patients had absent cortical responses following maximal EMS with biceps brachii in a relaxed state. At 12 months half the patients with responses following cortical stimulation ($n = 14$) who died of stroke-related death, were patients who required contraction to facilitate a response in biceps brachii. Note, however, most deaths occurred in patients in whom responses were not obtained on Day 1, even with muscle contraction ($n = 22$ for biceps brachii).

When the period of stay in hospital for patients with responses in relaxed biceps brachii at Day 1 was compared to patients with responses in biceps brachii only with muscle contraction, the mean stay was slightly longer (Table 50).

In conclusion, if responses can only be obtained at maximum levels of stimulation with the aid of muscle contraction, the outcome at 12 months is slightly less favourable than for patients with responses in relaxed muscles.

3.11 REASSESSMENT OF SURVIVORS AT 18 MONTHS

Functional and clinical assessments at 18 months after stroke of the 32 survivors from the first 60 patients recruited did not reveal any further changes of significance from the results obtained at 12 months. Therefore any further improvement after 12 months was minimal and all major changes in central motor conduction and recovery of motor function were complete. The choice of 12 months as the end point of the study appears to have been valid.

	DAYS IN HOSPITAL
Response obtained in relaxed biceps brachii	49.1 \pm 80.2
Response obtained only with contraction of biceps brachii	51.0 \pm 55.5
No Response obtained despite contraction of biceps brachii	86.5 \pm 84.9

Table 50. Relates the total length of time spent in hospital to ability to obtain a response in biceps brachii at Day 1 with the muscle relaxed or contracted (mean \pm S.D.).

3.12 VALIDITY OF CMCT AS A PREDICTOR OF OUTCOME.

The sensitivity and specificity of using CMCT as a predictor of outcome after stroke and the positive and negative predictive values are given in Table 51.

Sensitivity refers to the percentage of diseased subjects who have a positive test. In the context of this study, diseased subjects are the patients who have poor outcome at 12 months. The positive test refers to the patients with no responses following cortical stimulation i.e. the No Response Group. Specificity is the percentage of disease-free subjects who have a negative test. The disease-free subjects are those who have good outcome at 12 months with respect to particular outcome measures. The negative test refers to patients with responses following cortical stimulation i.e. the Delayed and Normal Response groups combined.

The statistical indices of sensitivity and specificity are useful in assessing the validity and informational value of a diagnostic test. However, positive predictive value (PPV) and negative predictive value (NPV) are not true indices of validity, because they depend on the relative proportions of diseased and disease-free subjects being tested. They are governed by the ratio of true and false positives (PPV) or true and false negatives (NPV). A test with high specificity (few false positives among the disease-free) can have low positive predictive value, if the ratio of the disease-free to diseased subjects is high. Similarly, a test with high sensitivity (few false negatives among the diseased) can have negative predictive value if the ratio of disease-free to diseased subjects is low (a very unlikely testing situation).

The results of this study show that the measurement of CMCT is a test of high specificity. The sensitivity is more variable for assessments at Day 1. The sensitivity was low for predicting poor outcome using the Barthel score and the probability of death. However, for most outcome measures identifying patients with no responses at Day 1 (positive test) had high positive predictive value.

The result of low positive predictive value relating to the Barthel score may have been different if a different score had been chosen to divide the patients arbitrarily into the two outcome groups of poor and good outcome. The positive predictive value relating to death is low because even though the proportion of patients in the No Response Group who die is high (52% for patients with no response in the thenar muscles at Day 1), a large minority of patients with no responses survive to 12 months. Only the assessment of Peg Test rate and assessment of muscle strength using the Motricity Index did not have a high negative predictive value for patients with responses at Day 1 (negative test) who have good outcome (disease-free). This is due to the fact that it is unusual for patients to fully recover normal motor function after stroke. In this study very few surviving patients at 12 months recovered normal dexterity and full strength as measured by the Peg Test rate and the Motricity Index. The test therefore has only a low rate of false negative results and is moderately good at identifying true positive results with respect to specific outcome measures.

In general the ability to identify two patient groups, those with responses (the Delayed and Normal Response Groups combined) and with no responses (the No Response Group) at Day 1 is a test with high specificity, with only a low rate of false negatives. (See: 4.8 Validity of CMCT as a predictor of outcome).

OUTCOME MEASURE	SENSITIVITY %	SPECIFICITY %	PPV %	NPV %
Tone in arm - abnormal	52	91	79	75
Tone in leg - abnormal	58	90	74	82
Motricity Index:				
Pinch grip - weak	48	95	89	67
Arm power - weak	44	92	84	64
Leg power - weak	50	89	74	75
Arm and leg power - weak	43	92	84	62
Peg test rate - < normal range	41	94	89	54
Barthel score - 12 or less	27	97	60	87
Rankin scale - dependent (3-5)	48	89	75	71
Stroke-related death by 12 months	64	74	53	81
All deaths by 12 months	57	74	55	76

TABLE 51. Sensitivity and specificity of responses in the thenar muscles to EMS of the motor cortex at Day 1 for defining different outcome measures at 12 months. PPV, positive predictive value; NPV, negative predictive value. In the Motricity Index weak is defined as any score less than full power for a particular movement or combination of movements. Values for the Nine-hole Peg Test are abnormal if they are outside the normal range defined by testing the 53 healthy subjects.

3.13 SUMMARY OF THE RESULTS RELATING TO THE PROGNOSTIC VALUE OF ASSESSING CENTRAL MOTOR CONDUCTION AFTER STROKE

Electromagnetic stimulation of the brain to evoke motor responses in the corticospinal tracts represents a simple, non-invasive neurophysiological method of assessing the function of the central motor pathways. The technique can be safely used in the first few days following stroke. The present study has demonstrated clinical and functional recovery following stroke correlates with the neurophysiological observations performed in the immediate post-stroke period of 12 -72 hours (median = 47.5 hours). The following observations were made:

Central motor conduction

1. In the period of 12 to 72 hours after stroke the integrity of the central motor pathways may be disrupted resulting in the absence of recordable responses following EMS of the motor cortex. If responses are obtained they may be delayed or within the normal CMCT range. Most patients who lack responses after stroke gain responses within three months. The latency of these responses is often prolonged but may eventually return to normal. Extension of stroke may lead to loss of responses.
2. The changes in central motor conduction were seen in both proximal and distal muscles with no difference between antagonistic muscles.
3. The durations of responses to cortical stimulation that appeared by 12 months were shorter than normal.
4. The thresholds to cortical stimulation in the damaged hemisphere were initially

elevated but they decreased to significantly lower levels than normal by 12 months. Similar, but less significant changes were seen for thresholds in the undamaged hemisphere. The threshold stimulation of both the damaged and non-damaged hemispheres for the thenar muscles was slightly lower than the value for biceps brachii.

5. At 12 months all major changes in central motor conduction were complete and no further changes were observed at 18 months.

Absent responses

1. Cortical responses were more likely to be absent in patients with infarctions, large lesions, lesions with mass effect or cortical lesions, as seen on CT scans.
2. Absent responses were more common in patients with Total Anterior Circulation Syndrome and patients with the greatest initial impairment of function.
3. Absent cortical responses indicated a poor prognosis leading to either death or incomplete functional recovery. 33 out of the 36 patients who died of stroke-related causes had some evidence of abnormal central motor conduction. The risk of death was greatest if responses were absent on Days 1-7 and if more than one muscle had absent responses.
4. By comparison to patients with responses at Day 1, patients with no responses who survived achieved significantly lower scores for all outcome measures at 12 months including abnormal tone and reflexes, muscle strength measured by the Motricity Index, hand dexterity measured by the Nine-hole Peg Test, activities of daily living measured by the Barthel score, functional independence measured by the Rankin scale and duration spent in hospital.

Delayed central motor conduction time

Patients with delayed responses did not regain normal hand dexterity. However, the overall recovery of these patients was comparable to those with responses with normal CMCT.

Normal central motor conduction time.

Patients with normal CMCT had a good prognosis. The probability of death was low and most survivors achieved good functional recovery.

The role of muscle contraction during the recording of responses.

Patients in whom cortical responses could only be obtained at maximal stimulation with the threshold-lowering effect of muscle contraction were at slightly higher risk of poor outcome compared to patients with responses obtained in relaxed muscles.

Specificity and sensitivity.

The measurement of CMCT is a test of high specificity. The sensitivity is more variable but there are factors relating to the design of the study which may account for the low sensitivity of some outcome measures.

Electromagnetic stimulation of the motor cortex in the immediate post-stroke period provides important prognostic information that relates to mortality and functional outcome at 12 months. The interpretation of the results, the possible mechanisms that might underlie the neurophysiological findings and the implications of these observations are discussed in the following chapter.

DISCUSSION.

4.1 OBSERVATIONS IN NORMAL SUBJECTS

The muscles studied included those acting at the shoulder, about the elbow and in the hand and involved spinal roots from C5 to T1. In the normal group of subjects the CMCTs calculated for each muscle were not significantly different, but the temporal distribution corresponded to the spatial cranio-caudal segmental distribution of the motor nuclei and therefore the conduction distance along the corticospinal pathway. When the values of CMCT for the group of normal subjects and for the non-paretic side of the stroke patients were taken together no statistical correlation of CMCT with age was found. The values are comparable to those observed in a cross-sectional study of children aged two years to adulthood (Eyre et al., 1991). The results of the present study support the observations made by Eyre et al. that CMCTs do not change in adult life. Therefore, when studying patients with stroke comparisons with normal adult subjects as a group are valid and there is no need to make any correction for age.

Macdonell et al. (1991), observed hemispheric threshold differences in MEPs produced by EMS. The threshold to stimulation of the left hemisphere projection to the muscles of the right hand was lower than that of the right hemisphere to left hand. It was proposed that the differences related to the asymmetry of corticomotoneuronal monosynaptic connections and the suggestion was made that a greater number project to the motor neurones of the right hand muscles than those of the left. The observations were made in only 19 right-handed normal subjects with recordings from the adductor digiti minimi and biceps brachii

muscles. In the present study handedness was not formally assessed and no hemispheric differences with respect to CMCT were discovered in the group of 53 normal subjects.

Macdonell et al. (1991) also observed that the threshold to stimulation of the hand muscles (adductor digiti minimi) was slightly lower than that of biceps brachii. The present study found the same minor differences when comparing the threshold to stimulation of the thenar muscles compared to biceps brachii in normal subjects.

4.2 OBSERVATIONS IN STROKE PATIENTS

The neurophysiology of conduction in the motor pathways from the cortex to the spinal cord has been investigated sequentially over 12 months in a group of 118 patients following stroke. At Day 1, defined as between 12 and 72 hours following the onset of symptoms, when the CMCT of responses obtained in stroke patients were compared to values of CMCT obtained from 53 healthy subjects, the patients divided into three groups those with normal CMCT, delayed CMCT and absent responses. All the target muscles investigated demonstrated a similar pattern of abnormality and recovery in terms of central motor conduction. In both normal subjects and stroke patients the target muscle was contracted or the homologous muscle of the contralateral limb was contracted in order to facilitate the response.

4.2.1 Comparison to other neurophysiological studies after stroke

Comparable neurophysiological observations after stroke have been made using SEPs (Larson et al., 1966; Kussofsky et al., 1982; La Joie et al., 1982; Macdonell et al., 1989; Zeman and Yiannikas, 1989) and using percutaneous ES of the brain (Berardelli et al., 1987; Thompson et al., 1987; Dominkus et al., 1990; Macdonell et al., 1989; Meyer et al., 1990; and Abruzzesse et al., 1991). A number of studies have now been completed using EMS (Bridgers, 1990; Ferbert et al., 1992 [patients with pontine infarction only]; Hömberg et al., 1991; Kandler et al., 1991; Chu and Wu, 1992; Escudero et al., 1992). In these studies only small numbers of patients were tested in the immediate post-stroke period and no comparisons were made to outcome at 12 months.

The present study observed changes in central motor conduction that had been reported in the studies cited above. Absent, delayed and normal responses were observed. The conduction abnormalities from dominant and non-dominant cerebral hemispheres were not significantly different. There was also no difference between CMCTs for distal compared to proximal muscles, and when the results of biceps brachii and its antagonist, triceps brachii were compared.

4.2.2 The importance of identifying responses in the immediate post-stroke period

It is significant that in approximately 15% of patients in the present study, responses could only be evoked by the facilitating action of muscle contraction. Escudero et al. (1992) made the same observation in some patients. Not all the

publications mentioned above include observations based upon responses recorded in contracted muscles. It is likely that the no response groups reported by Hömberg et al. (1991) and Kandler et al. (1991), where recordings were made in relaxed muscles, included a number of patients who might otherwise have been classed as responders. The conclusions drawn from these studies might have been different if all the patients had been identified in whom responses could be obtained by recording from muscles with the aid of muscle contraction.

Macdonell and Donnan (1992) found MEPs to be of prognostic value regardless of whether responses were obtained with or without contraction. The results of the present study suggest that it is essential to use muscle contraction during the recording of responses following cortical stimulation in order to identify all patients who are capable of responses. Our results suggest that patients with responses obtained only in the presence of contraction have a less favourable outcome compared to patients whose responses are present in relaxed muscles. However, the outcome of patients with no responses despite muscle contraction was considerably worse than patients with no responses in relaxed muscles but in whom responses could be evoked during muscle contraction. The results of the present study are therefore different to those reported by Macdonell and Donnan (1992). The authors did comment that if responses were only obtained with contraction the significance of the finding required further study.

The results of the present study compare favourably with the results of previous studies regarding the significance of identifying responses in patients immediately after stroke. Macdonell et al. (1989), Domininkus et al. (1990), and Chu and Wu (1992) all observed that, if responses to cortical stimulation were

obtained, this correlated with good outcome. These authors, with the exception of Chu and Wu (1992), also concluded that the absence of responses suggested a poor outcome. The present study clearly demonstrates the significance of identifying responses and the relationship of this finding to good outcome and the association of absent responses leading to poor outcome.

Chu and Wu (1992) observed a small number of patients who initially had no responses, but who regained them within a few weeks of stroke. The design of the present study allowed this phenomenon to be observed in close detail and clearly shows that most patients who had no responses immediately after stroke gain responses within three months. This is an important observation that casts doubt upon the validity of some of the conclusions made by Kandler et al. 1991; Hömberg et al. 1991; Ferbert et al. 1991; Chu and Wu 1992; Escudero et al. 1992, regarding the correlation of neurophysiological findings recorded many days or weeks after stroke with outcome.

The studies cited above lacked information regarding the evolution of central motor conduction changes and included only small numbers of patients tested in the acute stroke period. This may have resulted in inaccurate grouping of patients. Patients with responses many days after stroke may originally not have demonstrated responses if they had been investigated in the immediate post-stroke period. If responses were recorded in an individual and it was unknown whether responses had previously been absent, then the results in these patients are of limited value. Also, a greater number of patients with delayed CMCT were identified in many previous studies and this may indicate patients who originally had no responses but who have gained responses with delayed conduction. These

patients were therefore wrongly categorised as responders, which may explain the variable recovery of some patients in previous studies in whom responses were obtained and yet the outcome of the patient was poor. This weakens the conclusions made in previous publications regarding the prognostic significance of demonstrating responses after stroke.

The present study identified clearly patients who first lost and later regained responses by commencing investigations within hours of the onset of stroke and then sequentially retesting at fixed time intervals over 12 or 18 months after stroke. Patients in the present study who regained responses were identified in the post-stroke period as non-responders and were found to have a poor outcome. The results of the present study show that it is essential to identify all patients who have no responses and the only way of doing this is to investigate all patients at the earliest possible opportunity.

4.2.3 Responses with delayed CMCT

Escudero et al. (1992) found delayed responses were indicative of poor outcome. The present study identified only seven patients who initially had delayed CMCTs. In general this group of patients had an outcome comparable to the patients with normal CMCTs. There was a tendency towards poor return of hand dexterity as measured by the Nine-hole Peg Test, but the number of patients in this group was small and therefore the present study has not clarified the significance of delayed CMCT measures in the immediate post-stroke period.

4.2.4 Responses obtained following stimulation of the undamaged hemisphere

When the results of CMCT estimated from responses recorded in the non-paretic arm following stimulation of the undamaged hemisphere are compared to the results from normal subjects no differences were discovered. Therefore, the results of the present study agree with those of a number of authors (Thompson et al., 1987; Meyer et al., 1990; Beradelli et al., 1991; Hömberg et al., 1991; Escudero et al., 1992) who found responses in the paretic limb following stimulation of the non-damaged hemisphere had CMCTs within the normal range. The responses in the non-paretic limb can therefore act as controls for those of the paretic arm and indeed are indistinguishable from those of normal subjects.

4.2.5 The significance of the present study

The present study differs from those reported above in that the investigations were initiated within 12 to 72 hours after the onset of symptoms in a large and well-defined group of patients with first-ever stroke. The observations made in this study have helped to clarify a number of methodological features relating to the use of EMS following stroke. It is essential that investigations should commence as soon as possible after stroke in order to identify those who have no responses. Failure to do this leads to misleading results, if patients are first investigated a number of days after stroke when they may have regained responses. All cortical responses should be recorded during muscle contraction rather than in relaxed muscles in order to avoid inaccurate grouping of patients.

In some patients the clinical signs of stroke extend and become more widespread, often resulting in the subsequent loss of responses. Patients who originally demonstrate responses should therefore be retested seven days after the initial test in order to identify if there has been any subsequent loss of response. It is now clear why the initial observations of central motor conduction are so important. The absence of responses at any time carries the same poor prognosis as no response on Day 1 and leads to death or poor recovery. If responses are always present the functional prognosis is highly likely to be good.

At 18 months, a final review of the survivors from the first 60 patients recruited did not reveal any further features suggesting that recovery of motor function and its central nervous control was complete by 12 months.

4.3 THE REASONS FOR CHANGES IN CENTRAL MOTOR CONDUCTION

4.3.1 The pathophysiology of absent responses

The total absence of a response 12 months after stroke probably indicates the irreversible loss of the corticospinal projection to a particular motoneuronal cell group. It has been assumed that the responses are conducted by the corticospinal pathway projecting monosynaptically to spinal motoneurons. The arguments for corticospinal transmission are based upon the short latencies of the responses (Rothwell et al., 1991; Boyd et al., 1986) and observations in the monkey that EMS at levels above threshold excites corticospinal axons (Edgley et al., 1990b and 1992). In this study, if no response was recorded in one muscle in the upper limb, responses were often absent in other target muscles. This may result from

destruction of the corticospinal neurones or interneurones in the motor cortex, or damage to corticospinal axons in the pathway from the cortex to the synapse with α -motoneurones. In each case it is assumed that alternative pathways cannot be activated and that the threshold for corticospinal activation is not elevated above the output capability of the electromagnetic stimulator.

In the No Response Group at Day 1 responses to cortical stimulation were gained in a small number of subjects within a few days. However, the majority who gained responses did so by one month or occasionally by up to three months. This raises the question why recovery takes so long in the corticospinal pathway and whether conduction appears in descending pathways other than the direct crossed corticospinal pathway from cortex to spinal motoneurones. The hypothesis that recovery in stroke may be due to ipsilateral corticospinal pathways (Palmer et al., 1992) has not been supported by the findings of this study. In the present study the stimulator coil was held over the vertex. Although the direction of current flow in the coil governs which hemisphere is preferentially stimulated, the coil is capable of stimulating either hemisphere. It was therefore not possible to be sure in which hemisphere the evoked potential was produced. Attempts to produce ipsilateral responses by placing the coil over the ipsilateral hemisphere did not alter the latency of responses. The design of the present study did not allow the identification of alternative crossed or ipsilateral pathways.

4.3.2 The anatomical basis of absent responses

In the present study the correlations between the anatomical features of stroke visualised on CT scans and the underlying neurophysiology are of interest. The absence of responses correlated with large infarctions, lesions with mass effect and lesions involving the cortex. The CT scan results suggest lesions involving the cortex lead to loss of responses and purely subcortical damage was more probable to lead to retained responses, the reasons for this are unclear. However, the results from the present study agree with Escudero et al. (1992) who observed that responses were more likely to be absent if the lesion was cortical and large. Chu and Wu (1992) found cortical lesions to have a more variable association with absence of responses, but agreed with other studies that most delayed responses were associated with subcortical lesions (Abruzzesse et al., 1991; Beradelli et al., 1987; Dominkus et al., 1990; Thompson et al., 1991). The small number of patients with delayed responses at Day 1 in the present study do not allow accurate comparisons to be made between delayed CMCT and CT scans.

The correlations between CT scanning features and CMCT in the present study must be viewed carefully. It is not surprising that the correlations are not straightforward since the two techniques are evaluating very different aspects of the central nervous system. Scans provide anatomical information, whereas conduction studies are a measure of neurophysiological function of motor pathways. Also, the value of the CT scan is reduced by the fact that the investigation was not standardised. The scans were performed on two different machines. The procedure was performed whenever it was possible to scan the

patient, hence the scans did not take place at a fixed time after stroke, unlike cortical stimulation which was performed at fixed time intervals after stroke.

There is also the difficulty of interpreting the scan findings. Some of the earliest scans with no visible abnormality may have subsequently developed identifiable lesions. Oedema is often difficult to distinguish from infarction early after stroke and estimation of the boundaries of an infarct and approximations of size are therefore highly subjective. The correlation of CT scan appearances with central motor conduction was not straightforward particularly regarding the influence of mass effect. It is interesting that lesions involving the cortex compared to purely subcortical lesions had a higher probability of absent responses. This suggests that central motor conduction may be more prone to disruption when there is damage to the cortex resulting in cortical cell loss and disruption of cortical interneuronal connections.

4.3.3 The mechanisms underlying delayed central motor conduction

Delayed responses fell under two categories. At Day 1 a group of patients had delayed responses with relatively small discrepancies from the normal range. This was a small group with only seven patients with delays in the thenar muscles at Day 1 and only five survivors at 12 months. Patients with delayed central motor conduction had incomplete recovery of hand dexterity, but the significance of the observation remains unclear. A direct comparison of the outcome of the Delayed Response Group compared to the Normal Response Group failed to identify any significant differences despite the fact that the Delayed Response Group had a

lower mean outside the normal range. The size of the Delayed Response Group is too small and any statistical comparison with the other groups of patients may be inaccurate. A further group of patients with delayed CMCTs emerged in subsequent tests from amongst the non-responders at Day 1 who gained responses and from other individuals who extended their stroke, lost responses and then subsequently regained responses with prolonged CMCTs. Some patients who gained responses with delayed CMCT later developed responses with normal CMCTs, an observation that was also made by Chu and Wu, 1990.

Delayed responses in patients at Day 1 may reflect permanent loss of large diameter fast myelinated fibres in the corticospinal pathway. If the pathway was not destroyed, temporary slowing in the larger fibres may have been due to higher metabolic demands and a greater susceptibility to ischaemia (Branston et al., 1988). The possibility of this being a real phenomenon is highlighted in a number of studies (Momma et al., 1988; Oro and Levy 1987; Simpson et al., 1987). Dominkus et al. (1990) suggested an alternative view that a form of central motor neuropraxia may exist analogous to that following peripheral nerve damage. The net result would be slowing of conduction in the larger fibres or it is possible that the cortical stimulus is only able to activate smaller, more slow-conducting fibres under conditions of ischaemia.

4.3.4 Altered excitability of corticospinal neurones following stroke

In all stroke patients the threshold for eliciting responses from the damaged hemisphere was initially high, being greater than the range obtained in normal subjects, and decreased progressively during recovery. The thresholds fell over 12 months and in many cases were below the normal range (Table 23). The pathophysiology underlying this observation is difficult to explain. By 12 months following stroke the excitability of the spinal motoneurones, particularly those of flexors of the upper limb, is likely to be raised. Other monosynaptic inputs such as the stretch reflex evoke responses at much lower intensities and contribute to the clinical state of spasticity (Ashby and McCrea 1987). Raised motoneuronal excitability could arise through the reduction in spinal inhibitory mechanisms (Yanagisawa et al., 1976; Plant and Miller, 1990; Ashby and McCrea, 1987).

Conduction in the large myelinated fibres of the corticospinal pathway is thought to be responsible for the early component of the evoked motor responses following EMS of the motor cortex (Edgley et al., 1990b). These fibres may be more susceptible than small myelinated fibres to ischaemia. Since large myelinated axons in general have low thresholds to ES and fibre diameter in the corticospinal pathway is related to the threshold of EMS (Eyre et al., 1991), it would be expected that the threshold should rise following stroke. If the large myelinated fibres suffer partial and reversible conduction block following stroke, an initial increase and then decrease in the threshold of EMS would be expected. The temporary loss of large myelinated corticospinal fibres would also disrupt the temporal and spatial summation of direct and indirect volleys at the motoneurone

and contribute to the increase of threshold.

The initial increase of threshold for motor responses in muscles of the non-paretic limb following stimulation of the undamaged hemisphere was not unexpected but is probably due to processes such as general brain oedema and anatomical displacement of the hemispheres. The observation that the threshold to stimulation later in recovery and up to the final test sessions at 12 months **decreased** was not anticipated. There could be an increase in the excitability of corticospinal neurones or spinal motoneurones, but the underlying mechanisms are hard to define, particularly since reciprocal inhibition has been reported to be normal in the non-paretic arm (Miller and Plant, 1991).

The idea of altered excitability in the cortex is strengthened by the observation that some patients have responses only when facilitated with muscle contraction. This mechanism although thought to take place at the spinal level by some authors (Maertens de Noordhout et al., 1992) may still alter excitability of the pyramidal tract neurones or cortical interneurones at, or just before the initiation of movement. The lowering of cortical threshold by facilitation lowers the intensity of stimulation required to recruit multiple descending volleys and discharge motoneurones (Thompson et al., 1991). Altered excitability of the corticospinal neurones following stroke may explain why two patients in this study had movement in the pinch grip test in the Motricity Index assessment, despite the absence of responses in the thenar muscles on Day 1. On subsequent days these two patients had recordable responses and their outcome was better than patients with absent responses and no movement. The stimulus threshold to excite the cortex may have been exceptionally elevated above the maximum output intensity

of the stimulator.

4.3.5 Why should responses reappear?

A number of possibilities may explain why responses reappear. The first two mechanisms have already been discussed. Firstly, the corticospinal pathway may initially be refractory to the stimulus intensities used. The electrical currents induced in the cortex may not have been sufficient to excite the pathways in the damaged brain after stroke until, at a later date, the excitability of the cortex increased and the threshold to stimulation fell. A second possibility is that alternative motor pathways from the cortex to the spinal cord may have been activated particularly in the case of very prolonged responses that reappeared. These proposed pathways may be contralateral or ipsilateral.

A third explanation for the reappearance of responses with delayed CMCT could be the loss of myelinated fibres and dependency upon intact smaller fibres. There may have also been some demyelination of large fibres. Some patients lost responses and this was followed by the tardy return of responses that were initially delayed and subsequently fell to close or within the normal range, therefore the concept of reinnervation in the corticospinal tract must arise (Hömborg et al., 1991; Escudero, 1992). These patients had poor outcome and did not regain normal motor function. If reinnervation did occur it was therefore incomplete or, if it was anatomically complete, the final functional result was different since normal neurological function was not restored.

4.4 ALTERATION IN THE DURATION OF RESPONSES IN PATIENTS WHO GAIN RESPONSES

Patients who regained responses did so with shortened duration and usually of delayed CMCT. The measurement of duration from an average of single trials may possibly lead to a skew of the results by recording the shortest onset latency and the longest offset latency, but the inaccuracy is small in relation to the total duration. This phenomenon is possibly explained by the permanent loss of some of the fastest conducting fibres as a consequence of ischaemic damage. Their contribution to the response waveform is therefore the earliest and represents the initial component of the EMG response. Therefore if their function is impaired or lost or they undergo permanent conduction block, the initial component of the EMG response is late producing a delayed onset of the response and therefore delayed CMCT. The overall duration is less due to the loss of the contribution at the onset of the waveform assuming the slowest fibres continue to conduct normally.

4.5 THE RELATIONSHIP OF ABNORMALITIES IN CENTRAL MOTOR CONDUCTION AND INITIAL CLINICAL ASSESSMENTS

It is interesting that the symptoms that correlated with absent responses (weakness of limbs, swallowing difficulty, perception of visual problems, and urinary incontinence) reflect signs that are all known clinical predictors of poor outcome. There is an increased risk of death with dense limb paresis (Allen 1984) or leg weakness (Chambers et al., 1987), swallowing difficulty (Wade and Hewer

1987a), hemianopia (Gray et al., 1989), conjugate eye movement problems (Rankin, 1957; Oxbury et al., 1975) and urinary incontinence (Wade et al., 1985).

The relationship of central motor conduction to initial clinical assessments appears to be relatively straightforward. The highest proportion of patients with no responses were those with extensive hemispheric damage classified as total anterior circulation syndrome (TACS) in the Bamford scale. Patients with this constellation of signs have been shown to have an increased risk of poor outcome (Bamford et al., 1991). In patients with no responses, useful motor function of the affected limb was severely affected being either lost, resulting in no movement, or only a flicker of movement in the target muscle. This resulted in the inability to perform dexterous movements of the hand leading to a reduction in performance of many of the motor-related activities measured by the Barthel score at Day 7.

Electromagnetic stimulation of the motor cortex stimulates the corticospinal tracts. Therefore, if the normal function of the corticospinal tracts has been lost it is not surprising to find abnormalities in central motor conduction correlate with clinical signs of corticospinal tract damage in terms of changes in muscle power and tone, and abnormal plantar response. Delays in conduction, reflecting impaired function of the pathway were also accompanied by a reduction in the function of the target muscle with lower scores of power and dexterity. The lack of correlation of conduction abnormalities with initial examination of tendon reflexes probably is due to the effects of oedema and anatomical shift both of which may transiently produce these signs in the absence of permanent corticospinal damage.

4.6 THE PROGNOSTIC VALUE OF MEASURING CENTRAL MOTOR CONDUCTION AFTER STROKE

Abnormal central motor conduction after stroke

The main aim of this project was to evaluate the use of EMS of the brain to provide a numerical and objective method of providing an early prediction of motor outcome and mortality following stroke. The results strongly suggest that abnormal central motor conduction early after stroke is related to poor prognosis. Of the 36 patients who died of stroke-related causes, 31 had conduction defects producing absent responses in one or more muscles, on one or more occasions on Days 1-7 after stroke. In a further two patients with responses with normal CMCT, responses could only be obtained during muscle contraction. Investigations on Days 1-7 after stroke therefore identified abnormal conduction in 33/36 patients whose deaths were stroke-related. By contrast, only 3/55 patients with entirely normal central motor conduction died of stroke-related causes. Of the 76 survivors at 12 months 48 always had responses on Days 1-7 after stroke. 28 patients who had absent responses in one or more muscles, on one or more occasion on Days 1-7 survived. Only five of these 28 patients achieved independence as measured by the Rankin scale, the other 23 survivors all remained dependent.

The absence of responses in one or more muscles in the upper limb within 72 hours of stroke was an important observation. The greater the damage and the larger the number of muscles without responses, the greater the risk of poor outcome. An insult that can produce irreversible damage to the function of the corticospinal pathway represents a serious threat to the brain leading to incomplete

recovery of motor function or death. The fate of patients who lost conduction in the corticospinal pathway was profoundly worse than the patients with responses and they accounted for nearly all the stroke-related deaths. Therefore, the main discriminator relating to prognosis, is the ability to identify patients with responses compared to patients with no responses at Day 1. This is fortunate since it now provides the basis for an objective test.

Normal or delayed CMCT after stroke

The presence of responses did not guarantee recovery. When responses could only be obtained at maximal stimulus using the threshold lowering-effect of muscle contraction, this lead to a less favourable outcome (but statistically not significant). If responses were present but if CMCT was prolonged (Delayed Group), most of these patients survived but had incomplete return of hand dexterity. However, the outcome of this group of patients was not significantly different to the outcome of patients with normal CMCT. The vast majority of patients with responses survived. Their recovery was often incomplete, but the level achieved was considerably better than patients with no responses.

4.7 CLINICAL AND IMAGING METHODS OF PREDICTING OUTCOME COMPARED TO THE MEASUREMENT OF CENTRAL MOTOR CONDUCTION.

Assessment of the neurophysiological function of the central motor pathways after stroke can be safely performed in the immediate post-stroke period to provide valuable prognostic information. The results have been shown to correlate with mortality and to a wide range of clinical and functional abilities that depend upon the recovery of motor function of the upper limb. Unlike clinical and radiological assessments, the evaluation of central motor conduction provides an objective test with highly predictive data within hours of stroke.

The initial clinical signs, although relating to risk of death, can be ambiguous with respect to the recovery of motor skills. It is not until many days after the acute illness that the residual motor signs become accurate and predictive of functional outcome at 12 months. In comparison to clinical examination, assessment of central motor conduction was a more accurate method of predicting outcome. Clinical examination was able to identify patients with no movement in target muscles, suggesting a poor outcome. In most cases the absence of movement in a target muscle was associated with no recordable response to cortical stimulation thus suggesting a dense paresis and poor eventual outcome. However, within the group of patients with no movement in target muscles there was a subgroup of patients with recordable responses. The presence of responses with normal or delayed CMCTs implied that transmission in the corticospinal pathway was still present. The majority of patients with responses survived and had a high probability of a favourable functional outcome at 12 months. Predicting

the outcome for this group of patients would have been inaccurate using the findings from clinical examination.

Although CT scanning provides pathological and anatomical information that may be of prognostic value with respect to risk of death, it is not highly predictive of outcome of upper limb function. The investigation can not be performed by the bedside and therefore involves some discomfort to patients who are acutely ill. In the immediate post-stroke period there may be no visible lesion on the scan despite clinical signs suggestive of extensive damage. Even when lesions are visible on scans within hours of stroke they are often at an early stage of evolution and due to the influence of mass effect and oedema, measurements are often subjective leading to inaccurate and misleading prognosis.

The present study has shown that EMS of the brain is a valuable method of assessing the neurophysiological function of the corticospinal tracts after stroke. By combining the neurophysiological information with clinical assessments of function and anatomical and pathological data available from CT scanning it is now possible to provide a more accurate and earlier prognosis for individual patients.

4.8 VALIDITY OF CMCT AS A PREDICTOR OF OUTCOME

The high values for specificity in Table 51 imply that those patients with responses at Day 1 (Normal and Delayed Response Groups) have a greater probability of survival and good functional outcome at 12 months. This observation is supported by the tests of return of muscle power, manual dexterity, Barthel scores, Rankin scale and by mortality indices. Furthermore, the negative

predictive values (Table 51) emphasize that these patients are highly likely to achieve independence in activities of daily living, as judged by the Barthel and Rankin assessments and they are unlikely to die before 12 months.

The low values for sensitivity in Table 51 require more detailed explanation. At face value the figures imply that patients with no response at Day 1 have a mixed outcome, the majority having poor functional outcome at 12 months (See: Odds ratios - Fig. 14), but with some achieving good functional outcome and independence. In particular, it should be noted that the sensitivity is highest for death by 12 months and that it is the patients with no responses who account for most stroke-related deaths by 12 months. The sensitivity of measurements of CMCT in predicting functional outcome can be increased, when further tests are performed within the following seven days. For example, the sensitivity for tests performed at Day 1 with respect to stroke-related death at 12 months is 63.9% (specificity = 73.7), which rises to 77.8% (specificity = 68.4%), by expanding the No Response Group on Day 1, and including those who lose responses and therefore have no response on Day 3 or on Day 7. A similar improvement in sensitivity at the expense of specificity is seen for all the outcome measures. The net result is that the number of false negative results is reduced as the identification of patients with true positive results improves.

The low positive predictive value relating to the Barthel score might have been different if a different score had been chosen to divide the patients arbitrarily into the two outcome groups of poor and good outcome. A further reason may have been due to the fact that 12 patients died by Day 7 when the first Barthel scale was assessed. These 12 patients were therefore excluded from all

assessments using the Barthel score. The low positive predictive value relating to death is because even though the majority of patients die in the No Response Groups at Day 1 and Days 1-7, many patients with no responses survive to 12 months.

Only hand dexterity measured by the Nine-hole Peg Test and assessment of muscle strength using the Motricity Index did not have a high negative predictive value for patients with responses at Day 1 who have good outcome. This is due to the fact that very few stroke patients can be expected to regain normal motor function. Very few patients in this study at 12 months recovered normal dexterity and full strength as measured by the peg test rate and the Motricity Index.

4.9 THE USE OF THE THENAR MUSCLES FOR EVALUATION OF CORTICOSPINAL INTEGRITY

The function of the thenar muscles was assessed in terms of hand dexterity in the Nine-hole Peg Test, the strength of index finger to thumb pinch grip in the Motricity Index and indirectly assessed in a variety of manipulative skills assessed by the Barthel score and the Rankin scale. The function of the thenar muscles was therefore more comprehensively assessed than any other target muscle in terms of comparing how central motor conduction related to clinical function. The use of the thenar muscles in manipulation skills of the hand clearly identify them as a very important muscle group, the recovery of which is of the greatest importance to the patient. In the monkey, pinch grip appears to require the integrity of the corticospinal pathway (Lawrence and Kuypers, 1968). This is a highly evolved

action that is often observed clinically to be one of the most resistant parts of upper limb function to recover following stroke. It is therefore an important reflection of corticospinal function and motor recovery after stroke.

The sensitivity of assessing central motor conduction as a predictor of outcome can be sharpened by making observations in many muscles of the upper limb (See: Odds ratio for death - Fig. 14). However, if responses were to be recorded in only one muscle, the thenar muscles provide the best index, as can be judged from the tests of manual dexterity (Nine-hole Peg Test), activities of daily living (Barthel test), functional outcome (Rankin scale) and probability of death. This observation would be expected on the basis of functional testing in non-human primates, where lesions of the corticospinal pathway lead to permanent impairment of manipulative skills in adult and infant animals (Lawrence and Kuypers, 1968, Lawrence and Hopkins, 1976).

4.10 SAFETY OF ELECTROMAGNETIC STIMULATION AFTER STROKE

The possibility of EMS increasing the incidence of subsequent epileptic seizures in patients following stroke, was seriously considered at the onset of the study. The reported incidence of epilepsy following stroke varies in different studies, from 4.4% to 15% (Kilpatrick et al., 1990; Shinton et al., 1988; Louis and McDowell, 1967; Olsen et al., 1987; Black et al., 1983; Hauser et al., 1984), being highest (17%) for intracerebral haemorrhage (Berger et al., 1988). Isolated seizures following EMS in stroke patients with large areas of infarction have been reported (Hömborg and Netz, 1989; Fauth et al., 1992). These were likely to have

been incidental occurrences.

Only 2 (1.7%) patients in the present study had a seizure. This low incidence reflects the safety of the procedure and the inclusion criteria for the study, i.e. no patients had any known neurological disease including previous epilepsy and stroke. The Human Movement Research Group in Newcastle upon Tyne has wide experience in the use of EMS in children, including patients with epilepsy. Their results strongly suggest that the technique is safe, with no increased incidence of epilepsy despite years of follow-up (Miller and Eyre - personal communication). The experience based upon the present study using maximal EMS within the first few hours following stroke and repeatedly in patients with extensive cerebral damage, supports the view that the procedure is safe and does not provoke epilepsy. The technique is well-tolerated by ill patients and no adverse affects were reported during or after stimulation.

4.11 A PRACTICAL APPROACH TO THE USE OF EMS AFTER STROKE

The results of this study provide guidance for the future use of EMS in stroke patients. The safety restrictions used in this study should be applied, but epileptic seizures need not be regarded as an absolute contraindication for EMS in the light of its safe use in the patients with seizures or conditions associated with seizures. All potential subjects must be questioned about shrapnel injuries or other accidents leading to the presence of metal fragments in their face, eyes or brain. The risk of anatomical damage during EMS appears low, but the advent of more powerful and focused stimulators may possibly require a reassessment of the risks.

Responses should be recorded from a number of different muscles to provide a comprehensive record of corticospinal tract damage. However, recordings from the thenar muscles alone confer a high degree of prognostic information. The recording of responses should be assisted by muscle contraction. Initial investigations can be safely commenced immediately after stroke. Patients with no responses have a high probability of either death, or incomplete recovery of function. If responses are present the chance of survival and good functional outcome is good, but investigations should be repeated seven days after the first test to assess if the damage has progressed resulting in a poor prognosis if responses are subsequently lost. An alternative would be to reinvestigate only patients who clinically extend their stroke. If responses are present throughout the first seven days after stroke the prognosis is good. Responses in the paretic limb should be compared to normative data and can be compared to data recorded from the non-paretic limb, since the CMCTs do not differ from the range in normal subjects. There is no need to relate the CMCT results to the age of the patient in view of the consistency of CMCT throughout adult life.

4.12 CONCLUSIONS.

Measurement of central motor conduction is a safe test that provides important prognostic information. Two groups of patients can be easily identified within hours of stroke, those whose prognosis is exceptionally poor leading to death or at best, survival with major disability and long hospitalisation, and a second group whose chance of survival is high and whose recovery is likely to be

good. Neurophysiological assessment of central motor conduction using EMS provides information concerning the functional integrity of the corticospinal pathway which compliments clinical assessment of the patient and anatomical information from imaging of the brain. Combining the results of neurophysiological, clinical and anatomical assessments improves prognostication of an individual's prospects for survival and recovery following stroke. The implications of this are many.

4.13 THE FUTURE USE OF EMS FOLLOWING STROKE

Further studies to evaluate the use of this technique as an adjunct to clinical measures for predicting mortality and motor recovery after stroke are required. The findings of the present study should be verified by a similar independent large longitudinal study. There remains scope for further clarification regarding the importance of delayed CMCT immediately after stroke and the significance of responses that can only be obtained during muscle contraction. The value of measuring the amplitude of responses after stroke remains unclear and may merit further investigation. The use of EMS for predicting the outcome of lower limb function needs to be assessed now that more focused stimulator coils are available to evoke responses from leg muscles. The recovery of function in upper and lower limbs and mortality needs to be assessed for patients who have experienced multiple strokes.

Some patients with stroke have motor problems due to dyspraxia of motor function, incoordination from cerebellar dysfunction and sensory loss affecting motor activity. The role of EMS of the motor cortex and cerebellum after stroke in these very interesting groups of patients with motor impairment has not been established. The same procedures need to be assessed for patients with motor problems resulting from other forms of cerebral ischaemia in the form of subarachnoid haemorrhage and possibly patients with subdural haematomas.

The possibility that some recovery of motor function following stroke may be due to ipsilateral or other crossed motor pathways remains unknown. The activity of ipsilateral sensorimotor pathways may influence changes in central motor conduction and influence tone and reflexes following stroke. The development of spasticity may inhibit the recovery of normal motor function and it may be possible to investigate these changes in humans using EMS. It is also a possibility, given ethical approval, to investigate the influence of other motor pathways after stroke. Investigation of extrapyramidal pathways such as the vestibulospinal, rubrospinal and reticulospinal pathways in animal models of ischaemia using EMS in combination with direct and indirect ES of the brain may provide further information that can be applied to man.

The ability to identify patients with poor prognosis at a very early stage after stroke needs to be extended to assess how far the principles still hold if patients are investigated at the earliest possible time upon arrival in hospital, i.e. at 1-12 hours after stroke. Investigating patients at such an early stage after stroke would be a challenge and would present many procedural problems. However, if it could be confidently shown that a group of patients with exceptionally poor prognosis can be reliably identified within 1-12 hours of stroke then this could have major implications for drug trials. Whilst the efficacy of a drug needs to be evaluated using well-designed trials with very large numbers of subjects to provide clear results, there is still a need for pilot studies. Identifying a group of patients with little prospect of recovery and high risk of death could be used in pilot studies of ischaemia-protective drugs. Identifying patients within hours of stroke would be

within the therapeutic window of many proposed stroke treatments such as thrombolytic agents, calcium antagonists and glutamate receptor blockers, where treatment must be initiated within 12 hours or possibly as short as six hours after the onset of the stroke. Electromagnetic stimulation of the brain to provide information about the function of the corticospinal tracts could then be evaluated as a method of monitoring the therapeutic efficacy of ischaemia-protective drugs. The action of a drug to produce the return of normal central motor conduction and voluntary motor function in patients could be compared to an untreated group of patients. We already know the natural history of changes in central motor conduction and motor recovery of the untreated group from the results of the present study. If the recovery of the treated group was different and resulted in better outcome in terms of survival and recovery of motor function, EMS might prove to be useful in monitoring the efficacy of drugs used in stroke.

Studies are already underway to assess the use of monitoring central motor conduction during a variety of cerebral and spinal neurosurgical procedures. This concept of monitoring the corticospinal pathways during high-risk procedures that may lead to cerebral ischaemia could also be used in the context of coronary bypass, cerebrovascular or tumour surgery, or neuroradiological interventional therapy for the treatment of aneurysm or arteriovenous malformation. In all these procedures there is a major risk of stroke during the procedure. Intermittent monitoring of CMCT during the operation may provide additional information that would make the procedure safer.

The value of EMS in the context of rehabilitation following stroke is presently unknown. It is unknown how physiotherapy and other forms of therapy enhance relearning of motor skills. It may be possible using EMS to monitor the recovery of motor skills and to define whether such forms of physical therapy are of definite value. Studies are needed to identify whether more intensive therapy should be directed at patients with no responses following EMS in the hope of maximising what little improvement they achieve. One might argue that limited health care resources might be better employed by focusing upon those patients with responses following cortical stimulation since they appear to have the greatest potential for improvement. This would be at the expense of reducing the rehabilitation input to the patients with no responses following cortical stimulation. This controversial ethical question is worthy of further investigation.

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Scientific papers

Heald A, Bates D, Cartlidge NEF, French JM, Miller S.
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1. Natural history of central motor conduction.

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2. Central motor conduction measured within 72 hours after stroke as a predictor of functional outcome at 12 months.

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